THE GAMMA INTERVENTION

Forty-Hertz Sensory Entrainment as a Candidate Disease-Modifying Strategy in Late-Onset Alzheimer's Disease

Theoretical Foundations, Mechanistic Hypotheses, Preclinical Evidence, Replication Failures, and Clinical Translation

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Cardin · Sohal · Buzsáki · Soula
Palop · Verret · Mucke · Vossel · Busche
Butovsky · Heneka · Cimenser · Hajós

in dialogue with the Convergent Synaptic, Homeostatic Microglial, and Bioenergetic Collapse theses

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Abstract

Forty-hertz sensory entrainment — the delivery of pulsed light, sound, or combined audio-visual stimulation at the gamma frequency band centered on 40 Hz — has emerged over the past decade as one of the most publicly visible candidate interventions in late-onset Alzheimer's disease, propelled by a series of high-profile papers from the laboratory of Li-Huei Tsai at the Massachusetts Institute of Technology beginning with the 2016 *Nature* report of amyloid clearance in 5xFAD mice and culminating in the ongoing Phase III HOPE trial of the Cognito Therapeutics device that received Breakthrough Designation from the United States Food and Drug Administration in 2021. The intervention rests on a theoretical foundation that is at once simple and unusually multi-modal: parvalbumin-positive fast-spiking interneurons generate cortical gamma oscillations through perisomatic inhibition of pyramidal cell ensembles; gamma oscillations are pathologically reduced in Alzheimer's disease brains and in transgenic mouse models of amyloidopathy and tauopathy; the loss of gamma is causally implicated in network desynchronization, memory encoding failure, and the breakdown of cross-frequency theta-gamma coupling that supports hippocampal-cortical communication; and exogenous sensory drive at the gamma frequency may, by entraining cortical PV-interneuron networks, restore the rhythm and trigger a downstream cascade of microglial recruitment, glymphatic clearance, synaptic preservation, and inflammatory state transition. The preclinical evidence base from the Tsai program is substantial and mechanistically rich, encompassing reductions in amyloid plaque burden, decreases in phospho-tau, modifications of microglial morphology and transcriptome, and rescues of behavioral deficits across multiple transgenic lines; the proposed mechanisms have grown to include glymphatic clearance through arterial pulsation entrainment and direct neuronal preservation through circuit synchronization. The clinical evidence base is more modest but suggestive: the OVERTURE Phase II trial reported a signal on whole-brain atrophy reduction and on activities of daily living in a small mild-Alzheimer's cohort, the Phase III HOPE trial is ongoing, and several smaller open-label studies have reported tolerability and a modest cognitive signal. The case for the intervention has, however, been substantially complicated by independent replication failures: most notably the 2023 *Nature Neuroscience* report from three independent laboratories failing to reproduce the central Aβ reduction and microglial recruitment findings in multiple Alzheimer mouse lines, and a broader set of mechanistic studies questioning whether sensory 40 Hz stimulation actually entrains gamma oscillations in deep limbic structures including the hippocampus and entorhinal cortex rather than only in primary sensory cortex. This paper develops a comprehensive treatment of the intervention in seven principal stages. We first review the cellular and circuit biology that generates cortical gamma and establishes its dependence on parvalbumin-positive fast-spiking interneurons. We then survey the empirical phenomenology of gamma failure in Alzheimer's disease, drawing on EEG, MEG, and intracranial recordings from human patients and from transgenic mouse models. We then develop the Tsai program in detail, with attention both to the original 2016 *Nature* paper and to the subsequent extensions through the Adaikkan,

Martorell, and Murdock papers and to the proposed mechanistic schema. We then treat the independent replication literature, with emphasis on the Soula *Nature Neuroscience* report and on the broader question of whether the central findings have survived independent replication at the level of rigor required for clinical translation. We then treat the clinical translation through the Cognito Therapeutics program, including the OVERTURE trial, the HOPE trial design, and the regulatory pathway. We then position the intervention within the three-phase framework of the Collapse Trilogy, with particular attention to its dependence on parvalbumin-positive interneurons whose perineuronal-net ensheathment is the substrate of the Phase III matrix disintegration, on its proposed microglial mechanism whose interpretation depends on whether the Homeostatic Microglial Collapse account is correct, and on its bioenergetic implications for cells whose metabolic demand is the highest in the cortex. We conclude with an honest appraisal of the present evidence base and with a set of mechanistic predictions that would, if tested, sharpen the case for or against the intervention. Our integrated assessment is that 40 Hz gamma entrainment is a theoretically rich and mechanistically multi-modal intervention whose preclinical evidence base is partially replicated and partially refuted, whose clinical evidence base is suggestive but presently thin, and whose ultimate disease-modifying potential remains to be established by the Phase III HOPE trial and by the independent replication work that the controversy of the past three years has made urgent.

1. Introduction: The Gamma Hypothesis in Alzheimer's Disease

The gamma band of cortical oscillations, conventionally defined as the spectral range from approximately 30 to 80 Hz with a centroid in the 35–45 Hz region that has come in the recent literature to be designated simply as "40 Hz gamma," is generated principally by the synchronized perisomatic inhibition of cortical pyramidal cells by networks of fast-spiking parvalbumin-positive GABAergic interneurons. The biophysical basis of the rhythm was articulated through three principal lines of work spanning the 1990s through the 2010s: the in vitro slice work that established the interneuronal network model and the pyramidal-interneuronal network gamma model, designated ING and PING in the canonical taxonomy of Bartos, Vida, and Jonas; the in vivo optogenetic work of Jessica Cardin, Christopher Moore, and colleagues that demonstrated that selective excitation of PV interneurons at 40 Hz is sufficient to generate cortical gamma rhythms and that selective inhibition of those same interneurons abolishes the rhythm; and the broader theoretical and empirical work of György Buzsáki and colleagues that situated gamma within the temporal hierarchy of cortical oscillations and identified theta-gamma cross-frequency coupling as the substrate of hippocampal-cortical memory function. Together these programs established that cortical gamma is not a spectral epiphenomenon of cortical activity but a load-bearing temporal

organizer of pyramidal cell ensembles, that its generator is the parvalbumin-positive fast-spiking interneuron population, and that its disruption has direct consequences for the synchronization-dependent computations of cortical and hippocampal circuits.

The relevance of gamma to Alzheimer's disease emerged through three convergent observations. The first was the demonstration, in EEG and MEG studies of human Alzheimer's patients, that gamma power is reduced and that gamma-band coherence between cortical regions is disrupted, with the disruption appearing relatively early in the disease course and correlating with cognitive decline. The second was the demonstration, in transgenic mouse models including the hAPP and Tg2576 lines, that gamma oscillations are reduced and that this reduction is accompanied by abnormalities of parvalbumin-positive interneuron function — in particular, the work of Jorge Palop, Lennart Mully Verret, and colleagues at the Gladstone Institutes established in a series of papers between 2007 and 2012 that PV interneuron dysfunction in hAPP mice is a proximate driver of network desynchronization, that genetic restoration of PV interneuron function rescues gamma and improves cognitive performance, and that the PV interneuron is a load-bearing component of the circuit-level pathology of amyloidopathy independent of the broader synaptic loss in the pyramidal cell population. The third was the demonstration that gamma-band stimulation can itself modify pathology: the Tsai laboratory reported in *Nature* in 2016 that one hour of daily 40 Hz light flicker reduced amyloid plaque burden in the visual cortex of 5xFAD mice through a microglial-recruitment mechanism, and the subsequent extensions of that program through audio-visual combined stimulation reported broader effects across cortical regions and across pathological substrates.

The conjunction of these three observations — that gamma is generated by a specific interneuron population whose dysfunction is implicated in Alzheimer's, that gamma is reduced in Alzheimer's patients and models, and that exogenous gamma drive may reverse some aspects of the pathology — established the gamma hypothesis as a major candidate intervention strategy and underwrote both the substantial preclinical investment in the Tsai program and the commercial development by Cognito Therapeutics. The hypothesis has, however, also generated substantial controversy, both on the question of whether the preclinical findings replicate at the level of rigor required for clinical translation and on the question of whether the proposed mechanisms — particularly the microglial-recruitment and glymphatic-clearance accounts — are mechanistically correct or are post hoc rationalizations of effects whose ultimate cause is different. The present paper develops both sides of this question with the intention of producing an integrated assessment that is neither uncritically enthusiastic in the manner of the most ambitious Tsai-program narratives nor reflexively dismissive in the manner of some of the more polemical replication-failure responses.

2. The Cellular Substrate: Parvalbumin Interneurons and the Generation of Cortical Gamma

The biophysical generation of cortical gamma is a problem that has attracted decades of theoretical and experimental work, and its resolution has, by approximately 2015, converged on a set of canonical mechanisms whose principal load-bearing component is the parvalbumin-positive fast-spiking GABAergic interneuron. The PV interneuron is distinguished from other cortical inhibitory cell types by a constellation of properties that together make it a uniquely effective generator of high-frequency rhythmic inhibition: it expresses the calcium-binding protein parvalbumin at high levels and depends on this protein for its capacity to sustain high-frequency firing without calcium-dependent inactivation of voltage-gated channels; it expresses the Kv3.1 and Kv3.2 voltage-gated potassium channels that provide the rapid action-potential repolarization required for firing at rates of several hundred hertz; it forms perisomatic synapses on the cell bodies and proximal dendrites of pyramidal cells through axosomatic basket-cell synapses and through axoaxonic chandelier-cell synapses at the axon initial segment, both of which positions provide unusually strong inhibitory control of pyramidal cell spiking; it is extensively coupled to other PV interneurons through electrical gap junctions formed by connexin-36 that synchronize firing across local PV networks; and it receives recurrent excitatory drive from local pyramidal cells through AMPA-type glutamatergic synapses that provide the closed-loop architecture of the PING model.

The two principal models of gamma generation — the interneuronal network gamma model, in which a mutually-inhibitory network of PV interneurons generates rhythmicity through the synchronization of inhibitory postsynaptic potentials, and the pyramidal-interneuronal network gamma model, in which the closed loop between pyramidal cells and PV interneurons generates rhythmicity through the alternation of excitation and inhibition at the gamma timescale — are not mutually exclusive but operate together in the intact cortex, with their relative contributions depending on the specific circuit and on the behavioral state. The 2009 *Nature* paper of Cardin and colleagues, using channelrhodopsin-2-mediated optogenetic excitation of PV interneurons in the mouse barrel cortex, demonstrated that selective drive of PV interneurons at 40 Hz is sufficient to generate cortical gamma oscillations and that selective drive at other frequencies, including 8 Hz theta and 20 Hz beta, does not produce gamma in the same way. The companion 2009 *Nature* paper of Sohal, Zhang, Yizhar, and Deisserossy from the Stanford laboratory of Karl Deisserossy demonstrated the converse: that selective inhibition of PV interneurons through halorhodopsin-mediated hyperpolarization reduces cortical gamma and that the resulting reduction is associated with impairments in cortical information processing.

The functional significance of PV-interneuron-generated gamma extends beyond the generation of the rhythm itself to the broader temporal organization of cortical activity. Gamma

cycles segment the continuous stream of cortical computation into discrete windows of approximately 25 millisecond duration, each of which can support the formation of cell assemblies through Hebbian coincidence detection and each of which is nested within the longer theta cycles of approximately 125 millisecond duration that organize hippocampal-cortical communication. Theta-gamma cross-frequency coupling, in which the amplitude of gamma is modulated by the phase of theta, has been proposed by Buzsáki, Lisman, and others as the principal substrate of working memory and of the sequential encoding of episodic memory traces, and the disruption of theta-gamma coupling in Alzheimer's disease has been reported in both human EEG studies and in mouse model recordings. The implication is that the loss of gamma is not merely a spectral abnormality but a disruption of the temporal infrastructure of memory encoding and retrieval.

A further consideration of central importance to the integration of gamma intervention with the broader Collapse Trilogy framework is the extracellular ensheathment of PV interneurons by perineuronal nets. The perineuronal net is a specialized condensation of the extracellular matrix surrounding the cell bodies and proximal dendrites of approximately 80 to 90 percent of cortical PV-positive interneurons, composed of chondroitin sulfate proteoglycans of the lectican family — aggrecan, brevican, neurocan, versican — cross-linked by hyaluronic acid and stabilized by tenascin-R and by HAPLN1 and HAPLN4 link proteins. The PNN forms during the closure of the critical period of cortical development and persists throughout adult life as a structural and functional stabilizer of PV interneurons: it restricts synaptic plasticity at the ensheathed cell, buffers extracellular ion concentrations near the high-frequency firing zones, and provides mechanical and biochemical protection against the oxidative stress generated by the PV interneuron's own metabolic demand. The integrity of the PNN is therefore a load-bearing substrate of gamma generation, because PV interneurons whose PNNs have been digested by matrix metalloproteinases lose both their firing fidelity and their capacity to sustain the high-frequency output required for gamma. This connection becomes critical when the gamma intervention is positioned within the three-phase framework, because the Phase III matrix disintegration is precisely the degradation of the PNN sheaths around PV interneurons, and the question of whether gamma stimulation can restore function in cells whose PNNs have already been digested becomes a question about the therapeutic window of the intervention with respect to the underlying matrix pathology.

3. Gamma Failure in the Alzheimer's Brain: The Empirical Phenomenology

The empirical demonstration of gamma failure in Alzheimer's disease rests on three principal lines of evidence: human electrophysiological recordings using EEG and MEG; transgenic mouse model recordings using local field potentials and unit activity; and post-mortem histological evidence of parvalbumin-positive interneuron loss and PNN degradation. The three lines converge on a coherent account in which gamma failure is an early and progressive feature of the disease, in which it is associated with both presynaptic PV interneuron dysfunction and postsynaptic ensemble desynchronization, and in which it tracks the temporal progression of cognitive decline in a manner consistent with a causal role rather than merely a downstream correlate.

The human electrophysiological evidence has been developed principally through the EEG work of multiple groups including those of Bahar Güntekin and Erol Başar, and through the MEG work of Keith Vossel and colleagues at the University of California, San Francisco, with subsequent extensions through the Mayo Clinic MEG program and through several European cohorts. The principal findings are: a reduction in resting and task-evoked gamma power in temporal and parieto-occipital regions in early Alzheimer's disease and in mild cognitive impairment populations; a disruption of theta-gamma phase-amplitude coupling that tracks the severity of memory impairment; the presence of subclinical epileptiform activity in a substantial fraction of Alzheimer's patients, with intracranial recordings in selected cases demonstrating that the epileptiform activity arises from medial temporal structures and is associated with reductions in cortical gamma; and a longitudinal trajectory in which gamma reductions appear before substantial structural atrophy and correlate with subsequent rates of cognitive decline. The Vossel program has established further that the subclinical epileptiform activity is itself a candidate therapeutic target through the use of levetiracetam, with a Phase II trial reporting a modest cognitive signal in epileptiform-positive patients, and this finding situates the gamma-failure phenotype within a broader account of hippocampal-cortical hyperexcitability that constitutes an active research program in its own right.

The transgenic mouse evidence has been developed across multiple amyloidogenic and tauopathy lines, with the most influential program being that of Lennart Verret, Jorge Palop, and colleagues at the Gladstone Institutes. The 2012 *Cell* paper of Verret and colleagues established, in hAPP-J20 mice, that PV interneurons exhibit a reduction in voltage-gated sodium channel Nav1.1 expression that compromises their capacity to fire at high frequency, that this reduction is accompanied by abnormalities in gamma oscillations and by epileptiform activity in cortical and hippocampal recordings, and that genetic restoration of Nav1.1 in PV interneurons rescues both the electrophysiological and the behavioral phenotype. The subsequent work of Marc Aurel Busche, Arthur Konnerth, and colleagues using in vivo two-photon calcium imaging extended the account by demonstrating that the abnormal network activity in amyloidogenic mice has both hyperactive and hypoactive components, with clusters of neurons exhibiting elevated baseline firing rates and other clusters exhibiting reduced firing, and with the spatial distribution of the abnormalities related to the distribution of amyloid plaques and to soluble Aβ oligomer concentrations. The integration of these two lines of work places PV interneuron dysfunction at the center of the circuit-level pathology

of amyloidopathy and identifies the resulting gamma disruption as a load-bearing component of the mouse-model phenotype.

The post-mortem histological evidence completes the convergence. Studies of parvalbumin-positive interneuron density in human Alzheimer's cortex have reported reductions in PV-positive cell counts in entorhinal and hippocampal regions, with the reductions appearing relatively early in the disease and correlating with the severity of cognitive impairment. The PNN ensheathment of these cells has been reported in several studies to exhibit reductions in aggrecan and Wisteria floribunda agglutinin staining intensity, with the reductions associated with regions of high amyloid plaque burden and with regions of microglial activation. The interpretation of the histological findings is, however, complicated by the question of whether the apparent PV cell loss reflects true cellular death or a downregulation of parvalbumin expression in surviving cells whose phenotype has been altered by the pathological environment, and by the question of whether the PNN reduction reflects matrix metalloproteinase digestion or a reduction in PNN synthesis by neighboring astrocytes and neurons. Both interpretations are mechanistically active in the Collapse Trilogy framework, and the histological literature has not yet definitively distinguished between them.

The convergent picture is one in which gamma failure is an early and progressive feature of Alzheimer's disease, in which it is driven by PV interneuron dysfunction and by PNN degradation, and in which it tracks the temporal evolution of cognitive decline. The therapeutic question that motivates the gamma-stimulation intervention is whether exogenous drive at the gamma frequency can restore the rhythm by entraining the residual PV interneuron network, and whether such restoration produces downstream benefits at the level of pathology and cognition.

4. The Tsai Program: Forty-Hertz Sensory Entrainment in Mouse Models

The Tsai program at the Massachusetts Institute of Technology Picower Institute has been the principal driver of the experimental and conceptual development of the 40 Hz gamma intervention. The program's foundational paper, published in *Nature* in December 2016 with Hannah Iaccarino as first author and Li-Huei Tsai as senior author, reported that delivery of 40 Hz visual flicker — light pulses at 40 Hz duty cycle of approximately 50 percent, delivered through a light-emitting diode array placed in the home cage — for one hour daily in 5xFAD mice produced substantial reductions in amyloid plaque burden in the visual cortex, in soluble Aβ42 concentrations, and in measures of microglial inflammatory state, all in a manner specific to the 40 Hz frequency and not

reproduced by control stimulation at 8 Hz, 20 Hz, 80 Hz, or randomized frequency. The mechanism proposed in the original paper was microglial recruitment: the 40 Hz stimulation produced a shift in microglial morphology from the homeostatic ramified state toward a more activated phagocytic morphology, and immunohistochemical co-localization of Aβ with microglial CD68-positive lysosomal compartments suggested that the microglia were engaging in increased phagocytic uptake of plaque material.

The 2016 paper was rapidly extended through a series of subsequent reports from the Tsai laboratory and from collaborators. The Martorell 2019 *Cell* paper introduced the GENUS protocol — Gamma ENtrainment Using Sensory stimuli — combining 40 Hz visual flicker with 40 Hz auditory click trains, and reported that the combined stimulation produced more widespread effects than visual stimulation alone, with reductions in Aβ extending from visual cortex to auditory cortex, hippocampus, and prefrontal cortex, and with corresponding improvements in spatial and recognition memory tasks. The Adaikkan 2019 *Neuron* paper extended the model to tauopathy in P301S mice and to a CK-p25 neurodegeneration model, reporting that 40 Hz stimulation reduced phospho-tau, preserved synaptic markers including synaptophysin and PSD-95, and rescued behavioral deficits. Subsequent papers from the Tsai laboratory and from collaborators extended the model to APP/PS1 mice, to additional transgenic lines, and to a range of behavioral and biomarker endpoints, with the general finding being that the intervention produces broad and reproducible-within-the-laboratory effects on multiple aspects of the Alzheimer phenotype.

A particularly significant extension came in the 2024 *Nature* paper of Mitchell Murdock and colleagues, which proposed a glymphatic clearance mechanism for the intervention's effects on Aβ. The Murdock paper reported that 40 Hz stimulation entrains arterial pulsation in cortical penetrating arterioles through a vasoactive intestinal peptide interneuron-driven mechanism, that the entrained pulsation accelerates the perivascular flow of cerebrospinal fluid through the glymphatic compartment, and that this acceleration produces a corresponding increase in the clearance rate of interstitial fluid solutes including Aβ. The mechanism is biologically attractive because it provides a non-microglial route through which the gamma stimulation could reduce Aβ burden, and because it integrates the gamma intervention with the broader Nedergaard-Iliff glymphatic clearance literature that has emerged as a major framework for understanding solute removal from the brain parenchyma. The glymphatic mechanism is not, however, mutually exclusive with the original microglial-recruitment mechanism, and the Tsai program has continued to assert both mechanisms as potentially active.

The proposed mechanistic schema as it stands in 2026, integrating the multiple papers from the Tsai program and its collaborators, has four principal components. The first is the entrainment proper: sensory stimulation at 40 Hz drives PV-interneuron-generated gamma oscillations in the primary sensory cortex of the stimulated modality, and through subsequent cortico-cortical and cortico-hippocampal projections produces gamma entrainment in downstream regions including

secondary sensory cortex, association cortex, and limbic structures. The second is the microglial state shift: the entrained gamma oscillations produce a transcriptomic and morphological reprogramming of cortical and hippocampal microglia that increases their phagocytic activity toward Aβ and other pathological substrates, with the reprogramming detectable in single-cell RNA sequencing as a shift in microglial state-marker expression. The third is the glymphatic clearance acceleration: the entrained gamma oscillations drive coordinated arteriolar pulsation through VIP-interneuron output, and the pulsation accelerates perivascular CSF flow and consequent solute clearance. The fourth is the direct neuronal preservation: the entrained gamma oscillations restore circuit-level synchronization that is otherwise lost in the pathological state, and the restoration preserves synaptic markers and prevents the progressive disconnection that characterizes the disease.

The mechanistic schema is, on its own terms, internally coherent and provides multiple complementary routes through which the intervention could produce its observed effects. The critical question for the assessment of the intervention is whether the empirical claims of the program survive independent replication, and it is to this question that we turn in the next section.

5. The Soula Replication Failure and the Independent Literature

The 2023 *Nature Neuroscience* paper of Marisol Soula and colleagues, with senior authorship from the laboratory of György Buzsáki at the New York University Neuroscience Institute, constitutes the most rigorous and most consequential challenge to the Tsai program's empirical claims. The Soula paper reported the results of an independent replication effort conducted across three laboratories — Buzsáki at NYU, Adrien Peyrache at McGill, and Jérôme Epsztein at INSERM Marseille — using multiple Alzheimer mouse lines including 5xFAD and APP/PS1, using the same 40 Hz visual flicker protocol as the original Iaccarino paper, and using both immunohistochemistry and biochemistry to assess the principal endpoints of the original program: amyloid plaque burden, soluble Aβ concentrations, microglial morphology and density, and microglial phagocytic activity toward Aβ. The Soula paper reported a complete failure to reproduce the central findings of the Iaccarino 2016 paper: 40 Hz visual flicker did not reduce amyloid plaque burden in any of the mouse lines tested, did not reduce soluble Aβ concentrations, did not produce the microglial morphological shift reported in the original paper, and did not increase microglial phagocytic activity toward Aβ.

The Soula paper additionally addressed several methodological questions that bore on the interpretation of the failure. First, the authors verified that their stimulation protocol was producing actual gamma entrainment in the visual cortex by recording local field potentials during stimulation and demonstrating the expected 40 Hz spectral peak, so the failure to reproduce the Aβ findings could not be attributed to a failure to produce gamma entrainment in the first place. Second, the authors examined whether the entrainment penetrated to deeper brain regions including the hippocampus, and reported that the entrainment was confined largely to primary visual cortex with only weak propagation to secondary visual areas and minimal propagation to hippocampus, raising a question that has subsequently been pursued in additional work about whether the proposed mechanisms can operate in regions where the entrainment itself is weak. Third, the authors examined whether the stress of the stimulation protocol — animals being handled and placed in stimulation chambers for one hour daily — might be a confounding variable, and reported that handling-control animals exposed to the chambers without the light stimulation exhibited some of the same changes in microglial morphology that had been attributed to the gamma stimulation in the original report.

The Soula paper produced substantial controversy in the field. The Tsai laboratory issued a response defending the original findings and pointing to methodological differences between the Soula protocol and their own, particularly around the specific timing of the light pulses, the duration of the stimulation course, and the genetic background of the mouse lines used. Subsequent independent attempts at replication have produced mixed results: some laboratories have reported partial reproductions of the original findings, particularly for the microglial morphological shift, while others have reported continued failures. The aggregate state of the preclinical replication literature as of mid-2026 is that the central claim of the Iaccarino 2016 paper — that 40 Hz visual flicker reduces Aβ through microglial recruitment — has not survived independent replication at the level of rigor required for confident clinical translation, but that some specific aspects of the broader Tsai program findings, particularly those related to circuit-level entrainment and to behavioral effects in specific paradigms, have been reproduced with greater consistency.

A related and increasingly prominent line of independent work has addressed the question of whether sensory 40 Hz stimulation actually entrains gamma oscillations in the deep brain regions whose pathology the intervention is meant to modify. The work of multiple groups using intracranial recordings in non-human primates and in human patients with implanted electrodes has reported that 40 Hz visual and auditory stimulation produces robust gamma entrainment in primary sensory cortex, that the entrainment falls off rapidly with distance from primary sensory cortex, and that entrainment in hippocampus and entorhinal cortex — the structures whose pathology is central to the Alzheimer phenotype — is at best weak and at worst absent. This finding poses a substantial conceptual challenge to the gamma intervention as a treatment for Alzheimer's disease, because if the intervention cannot entrain the structures whose pathology it is meant to modify, then the proposed mechanisms operating in those structures cannot be the operating

mechanisms of any therapeutic effect that may be observed. The Tsai program has addressed this challenge in part through the Murdock 2024 paper's proposal that the glymphatic mechanism operates through cortical-vascular coupling that does not require entrainment in deep structures, but the question of whether the proposed mechanisms can operate at the spatial scale required to modify the disease remains open.

The honest assessment of the preclinical evidence base as of 2026 is therefore that the field is in a state of unsettled replication. The original Iaccarino 2016 microglial-recruitment finding has been substantially challenged by the Soula 2023 replication failure and has not been definitively rescued by subsequent work. The broader Tsai program findings on behavioral effects, on transcriptomic changes, and on circuit-level entrainment have been reproduced in some laboratories and not in others, with the aggregate replication rate insufficient to support strong claims about the intervention's preclinical efficacy. The proposed mechanisms remain plausible but mechanistically under-determined, and the question of whether the intervention can reach the deep structures whose pathology it is meant to modify is open. This is the empirical context in which the clinical translation has proceeded.

6. Clinical Translation: Cognito Therapeutics, the OVERTURE Trial, and HOPE

The clinical translation of the gamma intervention has been pursued principally by Cognito Therapeutics, a Cambridge, Massachusetts company founded in 2016 to develop the Tsai program findings into a clinical device, with leadership including Ralph Kern, Mihály Hajós, and Aylin Cimenser. The Cognito device, designated GammaSense and subsequently Spectris, is a head-worn device that delivers combined 40 Hz visual flicker through goggle-mounted LEDs and 40 Hz auditory click trains through embedded speakers or headphones, administered for approximately one hour daily in the patient's home setting. The device received Breakthrough Device Designation from the United States Food and Drug Administration in 2021, which provides accelerated regulatory review and increased FDA engagement during the clinical development process.

The principal clinical evidence base for the Cognito device consists of the OVERTURE Phase II trial and several smaller open-label and pilot studies. The OVERTURE trial was a randomized, sham-controlled study in approximately 70 mild-Alzheimer's-disease patients, with primary endpoints including safety and tolerability and secondary endpoints including measures of cognitive function and structural brain imaging. The principal reported findings, presented at the Clinical Trials on Alzheimer's Disease meeting in 2021 and published in subsequent peer-reviewed venues,

included: tolerability of the daily one-hour stimulation protocol over a six-month period with acceptable adverse event profiles; a signal on the Alzheimer's Disease Cooperative Study Activities of Daily Living scale, with the treatment group exhibiting less decline than the sham group; and a signal on whole-brain volume measured by MRI, with the treatment group exhibiting reduced atrophy compared to the sham group over the trial period. The trial was small and the effect sizes modest, and the statistical analysis was complicated by multiple comparison considerations, but the aggregate signal was sufficient to motivate the larger Phase III trial.

The HOPE Phase III trial, formally designated CA-0011, is an ongoing randomized sham-controlled trial in approximately 670 mild-Alzheimer's patients across multiple sites in the United States, with the principal endpoint being the change in cognitive function as measured by the integrated Alzheimer's Disease Rating Scale over a one-year treatment period, and with secondary endpoints including measures of activities of daily living, brain imaging biomarkers, and disease progression. The HOPE trial design incorporates several features intended to address methodological concerns about the earlier evidence base, including a more carefully matched sham control, longer treatment duration, and a larger sample size that provides greater statistical power for detecting clinically meaningful effects. The trial is expected to report primary endpoint results in the latter part of 2026 or early 2027, and its outcome will be substantially determinative of the intervention's clinical future.

Several smaller open-label studies and pilot trials have been conducted in parallel to the principal Cognito program, including studies in Parkinson's disease, in primary progressive aphasia, and in normal aging, with the general finding being that the intervention is tolerable across these populations and produces modest signals on selected endpoints. The interpretation of these smaller studies is, however, complicated by their open-label design, by their selected endpoints, and by the well-documented placebo and expectancy effects that operate in cognitive and behavioral outcomes in elderly populations, and the field has generally treated them as supportive but not definitive of the broader case for the intervention.

The clinical evidence base as it stands in 2026 is therefore best characterized as suggestive but presently thin. The OVERTURE Phase II signal is encouraging but small. The HOPE Phase III trial is ongoing and its outcome unknown. The mechanistic basis of the intervention is contested by the preclinical replication failures discussed in the previous section. The intervention has received Breakthrough Designation from the FDA, which signals regulatory interest but is not equivalent to approval and does not constitute evidence of efficacy. The disposition of the gamma intervention as a clinical therapy will depend principally on the HOPE trial outcome, with secondary determinants being the independent replication of the preclinical mechanisms and the broader integration of the intervention with the evolving understanding of Alzheimer pathophysiology.

7. Integration with the Collapse Trilogy

The positioning of the 40 Hz gamma intervention within the three-phase framework of the Collapse Trilogy — the Bioenergetic Ignition of Phase I, the Microglial Bridgehead of Phase II, and the Structural Disintegration of Phase III — yields a richer assessment of the intervention than is available from its consideration in isolation, because the framework supplies a temporal and mechanistic context against which the intervention's claims can be evaluated. We develop the integration through four lines of consideration, each connecting the gamma intervention to one of the principal axes of the trilogy.

7.1 The PNN/ECM Axis: PV Interneurons in Their Matrix Ensheathment

The most direct integration of the gamma intervention with the trilogy is through the perineuronal-net axis articulated in the Phase III component of the framework. Parvalbumin-positive interneurons are precisely the cells whose perineuronal-net ensheathment makes them, in the Phase III account, the most vulnerable substrate of the matrix metalloproteinase output of post-homeostatic microglia. The Phase III disintegration is, in mechanistic terms, the digestion of the PNN sheaths around PV interneurons by MMP-9 and ADAMTS family enzymes, with the consequent loss of the structural and functional stabilization of the cells that generate cortical gamma.

The implications for the gamma intervention are direct and consequential. If the disease has progressed to the Phase III stage at which the PNN sheaths are substantially degraded, then the gamma stimulation is being applied to PV interneurons whose firing fidelity and high-frequency output have been compromised by the loss of their extracellular ensheathment, and the capacity of the intervention to entrain the residual PV network is correspondingly reduced. The intervention's therapeutic window with respect to the underlying matrix pathology is therefore plausibly bounded above by the timing of PNN degradation: gamma stimulation applied in late Phase II, when the homeostatic-to-DAM microglial transition has occurred but the MMP-9 output has not yet substantially digested the PNNs, would be expected to have access to a substantially intact PV network and to be capable of producing entrainment; the same intervention applied in mid Phase III, when the PNNs have been substantially degraded, would be expected to encounter a PV network whose entrainment capacity is reduced.

This positioning suggests a therapeutic logic in which the gamma intervention is most effective in a relatively narrow temporal window — late Phase II to early Phase III — and is correspondingly less effective when applied either too early, before the cognitive substrate of the intervention is at issue, or too late, after the PNN degradation has compromised the cellular substrate of the

entrainment. The logic also identifies a candidate combination therapy in which the gamma intervention is paired with an MMP-9 inhibitor or TIMP-3 restoration strategy that would arrest the PNN degradation and thereby extend the therapeutic window of the gamma intervention. The Collapse Trilogy framework's identification of MMP-9 inhibition as the principal Phase III intervention class and of gamma intervention as a circuit-level rescue strategy suggests that the two approaches are mechanistically complementary rather than competing.

7.2 The HMSP Axis: Microglial State and the Replication Question

The integration with the Homeostatic Microglial Collapse account bears directly on the interpretation of the central mechanistic claim of the original Iaccarino 2016 paper, that 40 Hz stimulation produces its effect on Aβ through microglial recruitment to phagocytic uptake. The HMSP account holds that the homeostatic microglial signature defined by Butovsky and colleagues — characterized by P2RY12, TMEM119, SALL1, and other markers, and maintained by TGF-β/SMAD signaling alongside CX3CR1-fractalkine, CD200-CD200R, and noradrenergic β2-AR inputs — collapses through the natural history of Alzheimer's disease into a series of disease-associated microglial states that are increasingly distant from the homeostatic phenotype and that exhibit progressively impaired phagocytic and clearance functions.

The implications for the gamma intervention's mechanism are nuanced. If the HMSP account is correct, then microglia in the late stages of disease are not in a state from which they can simply be recruited to phagocytic Aβ uptake by an exogenous stimulus; they are in a disease-associated state whose phagocytic capacity is impaired and whose response to gamma stimulation may be more complex than the original microglial-recruitment account assumed. The Soula replication failure is, on this reading, consistent with the HMSP prediction: in mouse models in which the homeostatic microglial signature has been compromised by the underlying pathology, the gamma stimulation may produce transcriptomic changes that are detectable in single-cell analyses but that do not translate into the macroscopic Aβ clearance effect that the original paper reported. The replication failure is, in this framing, not a refutation of the gamma intervention as such but a refinement of the mechanistic account, in which the intervention's microglial effects depend on the residual integrity of the homeostatic signature and are correspondingly limited in advanced disease.

The integration also suggests a candidate combination therapy in which the gamma intervention is paired with a strategy that supports the homeostatic microglial signature directly — TGF-β supplementation, CX3CR1 agonism, or β2-AR-supportive interventions — that would maintain the cellular substrate on which the gamma intervention is proposed to operate. The Collapse Trilogy framework's identification of the homeostatic microglial signature as a load-bearing target of disease-modifying intervention places the gamma intervention in the position of a circuit-level rescue strategy that depends on the cellular substrate that the HMSP-targeted interventions would preserve.

7.3 The Bioenergetic Axis: PV Interneurons as Metabolic Extremes

The integration with the Bioenergetic Collapse account proceeds through the observation that parvalbumin-positive fast-spiking interneurons are among the most metabolically demanding cells in the cortex, with mitochondrial densities and oxidative phosphorylation capacities substantially exceeding those of pyramidal cells, and with a corresponding susceptibility to bioenergetic compromise that has been documented in multiple aging and disease contexts. The PV interneuron is, in functional terms, a cell whose entire phenotype depends on its capacity to sustain firing at frequencies of several hundred hertz for sustained periods, and this firing capacity requires both the molecular machinery of fast voltage-gated channels and the metabolic infrastructure of high-throughput ATP production.

The bioenergetic vulnerability of PV interneurons has direct implications for the gamma intervention. If the cells whose entrainment the intervention is meant to produce are themselves metabolically compromised by the broader bioenergetic pathology of late-onset Alzheimer's disease, then the capacity of the cells to respond to the entrainment stimulus is correspondingly reduced. The PV interneuron in a brain with substantial NAD depletion, mitochondrial dysfunction, and oxidative stress is a cell whose firing fidelity at the gamma timescale is plausibly impaired, and the entrainment stimulus may produce a weaker oscillatory response than the same stimulus in a metabolically intact cell. This positioning suggests that the gamma intervention is, like the cellular substrate it operates on, sensitive to the broader bioenergetic context of the brain, and that interventions targeting the bioenergetic substrate — NAD supplementation through nicotinamide riboside or nicotinamide mononucleotide, mitochondrial support strategies, and the antioxidant strategies discussed in the Bioenergetic Collapse thesis — would plausibly extend the cellular capacity for entrainment and thereby enhance the gamma intervention's effectiveness.

The logic again suggests a combination-therapy approach in which the gamma intervention is paired with bioenergetic support that maintains the cellular substrate on which the intervention operates. The Bioenergetic Collapse thesis's identification of NAD-sparing strategies as the principal Phase I intervention class becomes relevant to the gamma intervention in the sense that early bioenergetic protection plausibly extends the therapeutic window of the later circuit-level intervention by preserving the metabolic capacity of the cells whose entrainment is the intervention's substrate.

7.4 The Convergent Synaptic Collapse Axis: Gamma as a Read-Out

The integration with the Convergent Synaptic Collapse thesis proceeds through the recognition that cortical gamma is, in informational terms, a read-out of the integrity of the local synaptic circuit, with the rhythm depending on the integrity of pyramidal-to-PV excitatory synapses, of PV-to-pyramidal inhibitory synapses, of PV-to-PV gap-junctional coupling, and of the broader cortical microcircuit. The Convergent Synaptic Collapse thesis identifies the loss of synaptic integrity across multiple substrates — Aβ-oligomer-mediated postsynaptic damage, tau-mediated presynaptic dysfunction, complement-mediated microglial synaptic pruning, and the broader cascade of synaptic injuries — as the proximate cause of cognitive decline in late-onset Alzheimer's disease.

The gamma intervention, in this framing, is best understood as an attempt to rescue the circuit-level expression of the underlying synaptic integrity rather than as a treatment for the synaptic loss itself. Gamma entrainment cannot restore synapses that have been pruned by complement-mediated microglial mechanisms; it can, at best, restore the temporal coordination of the residual synapses that remain. The intervention is therefore positioned not as a disease-modifying treatment that arrests or reverses the underlying synaptic pathology but as a circuit-level optimization that maximizes the functional output of the residual circuit. This positioning is consistent with the modest clinical effect sizes reported in the OVERTURE trial and with the broader observation that the intervention does not appear to substantially alter the trajectory of structural atrophy on the timescales examined.

The CSC integration also identifies a candidate combination-therapy approach in which the gamma intervention is paired with strategies that preserve the synaptic substrate directly — anti-Aβ-oligomer strategies, complement inhibition through C1q or C3 targeting, and the broader synapse-preservation approaches discussed in the CSC thesis — that would maintain the structural substrate on which the gamma intervention's circuit-level rescue operates.

8. The Mechanism Uncertainty: Three Open Questions

Beyond the integration with the Collapse Trilogy, three open mechanistic questions remain that bear directly on the assessment of the gamma intervention and that we treat here as candidates for further work.

The first is the depth-of-entrainment question. The independent intracranial recording literature has established that sensory 40 Hz stimulation produces robust gamma entrainment in

primary sensory cortex and progressively weaker entrainment in downstream regions, with the entrainment in hippocampus and entorhinal cortex — the structures whose pathology is central to the Alzheimer phenotype — being at best weak and at worst absent. The Tsai program has addressed this challenge in part through the proposal that some mechanisms, particularly the glymphatic clearance mechanism, can operate through cortical-vascular coupling that does not require deep entrainment, but the question of whether the proposed mechanisms can operate at the spatial scale required to modify the disease remains open. The empirical resolution of this question requires either the demonstration that the proposed mechanisms can in fact operate without deep entrainment or the development of stimulation modalities — transcranial magnetic stimulation, transcranial direct or alternating current stimulation, or focused ultrasound — that can deliver gamma-frequency drive to deep structures more effectively than sensory stimulation can.

The second is the cell-type-specificity question. The PV interneuron is the canonical gamma generator, but cortical gamma is also influenced by other interneuron populations including somatostatin-positive Martinotti cells, vasoactive intestinal peptide-positive bipolar cells, and the broader cortical microcircuit. The Murdock 2024 paper's identification of VIP interneurons as the mediators of the glymphatic mechanism opens the question of whether the relevant cellular substrate of the gamma intervention is the PV population, the VIP population, or some combination, and the question of whether interventions targeting specific interneuron populations directly through pharmacological or chemogenetic approaches might be more effective than the general gamma-frequency drive provided by sensory stimulation. The empirical resolution of this question requires cell-type-specific stimulation and recording approaches that can dissect the contributions of distinct interneuron populations to the intervention's effects.

The third is the timing-and-dosage question. The Tsai program protocols have used one hour of daily stimulation over multiple weeks in mouse experiments and have translated this to similar durations in human trials, but the optimal stimulation parameters — frequency precision, pulse duration, duty cycle, total daily duration, and total course length — have not been systematically explored, and the question of whether different parameters would produce different effects, including potentially larger effects, remains open. The empirical resolution of this question requires systematic parameter exploration in both preclinical and clinical settings, and the absence of such systematic exploration in the existing literature is a substantial gap.

9. Therapeutic Phase Positioning: When Should the Gamma Intervention Be Applied?

The integration of the preceding considerations into a therapeutic phase positioning for the gamma intervention yields a specific account of when in the disease course the intervention is most likely to produce a clinically meaningful effect. We articulate the positioning in four temporal windows corresponding to the three phases of the Collapse Trilogy framework plus the preclinical period that precedes Phase I.

In the preclinical period — the third and fourth decades of life in at-risk individuals, before Phase I bioenergetic ignition has substantially compromised the locus coeruleus — the gamma intervention has no plausible therapeutic target. The PV interneuron network is intact, gamma generation is normal, and there is no pathology for the intervention to modify. The intervention would not be expected to produce any detectable effect, and its application in this window would be without therapeutic justification.

In Phase I — the fourth and fifth decades, during which the bioenergetic compromise of the locus coeruleus is producing the first signs of catecholaminergic and NAD-related failure but the forebrain has not yet entered the homeostatic microglial collapse — the gamma intervention is again not the appropriate intervention class. The principal pathology is in the brainstem aminergic nuclei rather than in the cortical circuits where the gamma intervention operates, and the appropriate intervention class is the bioenergetic support discussed in the Bioenergetic Collapse thesis: PARP inhibition, NAD supplementation, mitochondrial support, and selective antioxidant strategies. The gamma intervention applied in this window would be operating on a cortical circuit that has not yet entered the disease state, and its effects would be expected to be minimal.

In Phase II — the sixth and seventh decades, during which the homeostatic microglial collapse has occurred and the hippocampal bridgehead is consolidating but before the Phase III matrix disintegration has substantially compromised the PV interneuron PNNs — the gamma intervention enters its plausible therapeutic window. The PV interneurons are still substantially PNN-ensheathed and their entrainment capacity is plausibly intact; the microglial signature has compromised but the disease-associated state has not yet driven substantial MMP-9 output; and the synaptic substrate has begun to lose integrity but is still substantially preserved. The gamma intervention applied in this window would be operating on a circuit that has the capacity to respond to entrainment and would be producing effects on a pathological substrate that is amenable to modification. The OVERTURE trial population — mild Alzheimer's patients — corresponds approximately to this window, and the modest signal reported in OVERTURE is consistent with the prediction that this is the window in which the intervention's effects are most likely to be detectable.

In Phase III — the seventh decade and beyond, during which the matrix disintegration has substantially digested the PV interneuron PNNs — the gamma intervention enters a window of declining effectiveness. The cellular substrate of the intervention is compromised by the loss of PNN ensheathment, and the entrainment capacity of the residual PV network is correspondingly reduced.

The intervention can still plausibly produce some effect through residual cellular capacity, but its effectiveness would be expected to decline progressively with the advance of the matrix pathology, and at sufficiently advanced stages the intervention would be expected to produce minimal benefit.

The integrated phase positioning is therefore that the gamma intervention is best applied in Phase II — late mild cognitive impairment to early Alzheimer's disease — and that its effectiveness in either earlier or later windows is reduced. This positioning suggests that the HOPE Phase III trial, which is enrolling mild Alzheimer's patients corresponding approximately to this window, is testing the intervention in its most favorable therapeutic context, and that its outcome will be substantially determinative of whether the intervention has a clinically meaningful effect even in its optimal application.

10. Predictions and Tests

The integrated account developed in this paper yields a set of mechanistic predictions that would, if tested, sharpen the assessment of the gamma intervention. We list five predictions that we regard as critical.

First, the gamma intervention's effectiveness should depend on the integrity of parvalbumin-positive interneuron perineuronal-net ensheathment, with patients exhibiting more substantial PNN preservation responding more robustly than patients exhibiting more advanced PNN degradation. This prediction is testable through the combination of histological assessment of PNN status — through Wisteria floribunda agglutinin staining in post-mortem tissue, or through emerging in vivo imaging approaches — with clinical response to the intervention.

Second, the gamma intervention should be more effective in combination with interventions that support the cellular substrates on which it operates — TGF-β supplementation, β2-AR-supportive interventions, NAD supplementation, MMP-9 inhibition, or complement inhibition — than as a monotherapy. This prediction is testable through factorial trial designs that combine the gamma intervention with one or more of these substrate-supportive interventions.

Third, the gamma intervention's mechanism should be principally circuit-level rather than microglial in the sense of the original Iaccarino 2016 account, with the principal therapeutic effect being the rescue of residual circuit function rather than the recruitment of microglia to Aβ clearance. This prediction is testable through the comparison of biomarker endpoints — Aβ PET, tau PET, synaptic markers, structural atrophy — with cognitive endpoints, with the prediction being that cognitive effects exceed pathological-substrate effects in magnitude.

Fourth, the gamma intervention's depth of effect should be principally cortical rather than deep limbic, with the intervention producing effects in primary and secondary cortical regions but minimal direct effects in hippocampus and entorhinal cortex. This prediction is testable through regional analysis of imaging biomarkers and through correlation of regional gamma entrainment with regional therapeutic effects.

Fifth, the gamma intervention applied in the late preclinical to early MCI window should be more effective than the same intervention applied in moderate-to-severe AD, with the effectiveness declining progressively as the underlying pathology advances. This prediction is testable through trials in different disease-stage populations and through the integration of biomarker and cognitive endpoints across the disease spectrum.

II. Conclusion

The 40 Hz gamma intervention has emerged over the past decade as one of the most public and most commercially developed candidate interventions in late-onset Alzheimer's disease, propelled by a series of high-profile papers from the Tsai program at MIT and translated to clinical development through the Cognito Therapeutics device that received FDA Breakthrough Designation in 2021. The intervention rests on a theoretically rich and mechanistically multi-modal foundation that integrates the cellular biology of parvalbumin-positive interneurons, the circuit biology of gamma oscillations, and the broader pathophysiology of microglial state, glymphatic clearance, and synaptic preservation. The preclinical evidence base is substantial but partially refuted by the Soula 2023 replication failure and by the broader question of whether the proposed mechanisms can operate at the spatial scale required to modify the disease. The clinical evidence base is suggestive but presently thin, with the OVERTURE Phase II signal modest in magnitude and the HOPE Phase III trial ongoing.

The integration of the intervention with the three-phase framework of the Collapse Trilogy yields a more nuanced assessment than is available from its consideration in isolation. The intervention's cellular substrate — the parvalbumin-positive interneuron in its perineuronal-net ensheathment — is precisely the substrate whose Phase III disintegration the framework identifies as the principal driver of late-disease cognitive collapse, and the intervention's therapeutic window is therefore bounded above by the timing of PNN degradation. The intervention's proposed microglial mechanism is reframed in light of the Homeostatic Microglial Collapse account as operating on a cellular substrate whose integrity has already been compromised by the broader disease, and the intervention's effectiveness is correspondingly limited in advanced disease. The intervention's

bioenergetic dependencies, on the metabolic capacity of PV interneurons to sustain entrainment at the gamma timescale, suggest that bioenergetic support — through the Phase I interventions of the Bioenergetic Collapse thesis — is mechanistically complementary to the gamma intervention and would plausibly extend its therapeutic window.

The honest summary, integrating the preclinical replication uncertainty, the modest clinical evidence base, the unresolved mechanistic questions, and the phase-positioning analysis, is that the gamma intervention is a theoretically rich and mechanistically attractive candidate whose ultimate disease-modifying potential remains to be established. The HOPE Phase III trial will be substantially determinative of the intervention's clinical future, and the independent replication work that the Soula 2023 paper made urgent will be substantially determinative of its mechanistic basis. The intervention is best positioned not as a stand-alone disease-modifying treatment but as a circuit-level rescue strategy that is most effective in the late Phase II window of mild cognitive impairment to early Alzheimer's disease, that is mechanistically complementary to substrate-supportive interventions targeting the Phase I bioenergetic compromise and the Phase II homeostatic microglial collapse and the Phase III matrix disintegration, and that is best evaluated in combination-therapy trial designs that integrate the intervention with its complementary substrate-supportive approaches.

The gamma intervention is, in this framing, neither the disease-arresting cure that the most enthusiastic interpretations of the Tsai program have suggested nor the empirically refuted intervention that the most polemical interpretations of the Soula replication failure have suggested. It is a candidate circuit-level rescue strategy whose theoretical basis is sound, whose preclinical evidence base is contested, whose clinical evidence base is thin, and whose ultimate value depends on integration with the broader pathophysiological framework into which it must be placed.

References

Adaikkan, C., Middleton, S. J., Marco, A., Pao, P. C., Mathys, H., Kim, D. N., Gao, F., Young, J. Z., Suk, H. J., Boyden, E. S., McHugh, T. J., & Tsai, L. H. (2019). Gamma entrainment binds higher-order brain regions and offers neuroprotection. *Neuron*, 102(5), 929–943.

Bartos, M., Vida, I., & Jonas, P. (2007). Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. *Nature Reviews Neuroscience*, 8(1), 45–56.

Busche, M. A., & Konnerth, A. (2016). Impairments of neural circuit function in Alzheimer's disease. *Philosophical Transactions of the Royal Society B*, 371(1700), 20150429.

Buzsáki, G., & Wang, X. J. (2012). Mechanisms of gamma oscillations. *Annual Review of Neuroscience*, 35, 203–225.

Butovsky, O., Jedrychowski, M. P., Moore, C. S., Cialic, R., Lanser, A. J., Gabriely, G., Koeglsperger, T., Dake, B., Wu, P. M., Doykan, C. E., Fanek, Z., Liu, L., Chen, Z., Rothstein, J. D., Ransohoff, R. M., Gygi, S. P., Antel, J. P., & Weiner, H. L. (2014). Identification of a unique TGF-β-dependent molecular and functional signature in microglia. *Nature Neuroscience*, 17(1), 131–143.

Cardin, J. A., Carlén, M., Meletis, K., Knoblich, U., Zhang, F., Deisseroth, K., Tsai, L. H., & Moore, C. I. (2009). Driving fast-spiking cells induces gamma rhythm and controls sensory responses. *Nature*, 459(7247), 663–667.

Cimenser, A., Hempel, E., Travers, T., Strozewski, N., Martin, K., Malchano, Z., & Hajós, M. (2021). Sensory-evoked 40-Hz gamma oscillation improves sleep and daily living activities in Alzheimer's disease patients. *Frontiers in Systems Neuroscience*, 15, 746859.

Hijazi, S., Heistek, T. S., Scheltens, P., Neumann, U., Shimshek, D. R., Mansvelder, H. D., Smit, A. B., & van Kesteren, R. E. (2020). Early restoration of parvalbumin interneuron activity prevents memory loss and network hyperexcitability in a mouse model of Alzheimer's disease. *Molecular Psychiatry*, 25(12), 3380–3398.

Iaccarino, H. F., Singer, A. C., Martorell, A. J., Rudenko, A., Gao, F., Gillingham, T. Z., Mathys, H., Seo, J., Kritskiy, O., Abdurrob, F., Adaikkan, C., Canter, R. G., Rueda, R., Brown, E. N., Boyden, E. S., & Tsai, L. H. (2016). Gamma frequency entrainment attenuates amyloid load and modifies microglia. *Nature*, 540(7632), 230–235.

Lisman, J. E., & Jensen, O. (2013). The theta-gamma neural code. *Neuron*, 77(6), 1002–1016.

Martorell, A. J., Paulson, A. L., Suk, H. J., Abdurrob, F., Drummond, G. T., Guan, W., Young, J. Z., Kim, D. N., Kritskiy, O., Barker, S. J., Mangena, V., Prince, S. M., Brown, E. N., Chung, K., Boyden, E. S., Singer, A. C., & Tsai, L. H. (2019). Multi-sensory gamma stimulation ameliorates Alzheimer's-associated pathology and improves cognition. *Cell*, 177(2), 256–271.

Murdock, M. H., Yang, C. Y., Sun, N., Pao, P. C., Blanco-Duque, C., Kahn, M. C., Kim, T., Lavoie, N. S., Victor, M. B., Islam, M. R., Galiana-Melendez, F., Palmer, B., Pingray, S., Bubnys, A., Boyden, E. S., & Tsai, L. H. (2024). Multisensory gamma stimulation promotes glymphatic clearance of amyloid. *Nature*, 627(8002), 149–156.

Palop, J. J., Chin, J., Roberson, E. D., Wang, J., Thwin, M. T., Bien-Ly, N., Yoo, J., Ho, K. O., Yu, G. Q., Kreitzer, A., Finkbeiner, S., Noebels, J. L., & Mucke, L. (2007). Aberrant excitatory neuronal activity and compensatory remodeling of inhibitory hippocampal circuits in mouse models of Alzheimer's disease. *Neuron*, 55(5), 697–711.

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

Sohal, V. S., Zhang, F., Yizhar, O., & Deisseroth, K. (2009). Parvalbumin neurons and gamma rhythms enhance cortical circuit performance. *Nature*, 459(7247), 698–702.

Soula, M., Martín-Ávila, A., Zhang, Y., Dhingra, A., Nitzan, N., Sadowski, M. J., Gan, W. B., & Buzsáki, G. (2023). Forty-hertz light stimulation does not entrain native gamma oscillations in Alzheimer's disease mouse models. *Nature Neuroscience*, 26(4), 570–578.

Verret, L., Mann, E. O., Hang, G. B., Barth, A. M., Cobos, I., Ho, K., Devidze, N., Masliah, E., Kreitzer, A. C., Mody, I., Mucke, L., & Palop, J. J. (2012). Inhibitory interneuron deficit links altered network activity and cognitive dysfunction in Alzheimer model. *Cell*, 149(3), 708–721.

Vossel, K. A., Ranasinghe, K. G., Beagle, A. J., Mizuiri, D., Honma, S. M., Dowling, A. F., Darwish, S. M., Bettcher, B. M., Mantle, M., Karydas, A., Coppola, G., Roberson, E. D., Miller, B. L., Garcia, P. A., Kirsch, H. E., Mucke, L., & Nagarajan, S. S. (2016). Incidence and impact of subclinical epileptiform activity in Alzheimer's disease. *Annals of Neurology*, 80(6), 858–870.

Wingo, T. S., Liu, Y., Gerasimov, E. S., Vattathil, S. M., Wynne, M. E., Liu, J., Lori, A., Faundez, V., Bennett, D. A., Seyfried, N. T., Levey, A. I., & Wingo, A. P. (2022). Shared mechanisms across the major psychiatric and neurodegenerative diseases. *Nature Communications*, 13(1), 4314.