Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Gamma (40 Hz) Stimulation

Evidence Summary

Gamma stimulation can enhance functional connectivity in brain networks, but its ability to impact clinical outcomes remains to be seen. Personalization of gamma frequency may be needed.

Neuroprotective Benefit: Gamma stimulation may enhance performance on specific cognitive tasks related to the brain network engaged by stimulation, but clear impacts to global cognition or brain pathology have not been clinically observed thus far.

Aging and related health concerns: Gamma wave stimulation is directed toward modulation of brain function and used primarily for neurological conditions.

Safety: Gamma stimulation is generally safe and well-tolerated. Sensory stimulation may induce tinnitus, headache, fatigue, and eyestrain. Electrical stimulation may induce temporary burning/stinging at stimulation sites, headache, and visual disturbances.

Availability: Currently being tested in clinical trials, but many consumer devices are available for purchase.	**Dose**: Not established. The vast majority of studies use a paradigm of 40 Hz stimulation one hour per day.	**Chemical formula:** N/A **MW**: N/A
Half-life: N/A The effects of a single session of gamma stimulation on brain function are transitory.	**BBB**: Gamma stimulation can modulate brain activity.	
Clinical trials: Gamma stimulation has been tested in dozens of small, mostly proof-of-concept studies in cognitively healthy and cognitively impaired populations using sensory stimulation (audio/visual/tactile) and/or electrical stimulation (primarily tACS).	**Observational studies**: Gamma oscillations are associated with cognitive function, and have been shown to be dysregulated in neurodegenerative disease and neuropsychiatric disorders.	

What is it?

Gamma stimulation is a form of neuronal modulation that is designed to strengthen endogenous neuronal oscillations in the gamma frequency range [1]. These oscillations represent the propagation of neuronal activity throughout brain networks. These brain waves can be produced at different frequencies, and these rhythms are associated with different brain functions/cognitive processes. The lowest frequency waves, called delta (1 to 4 hertz [Hz]) occur during deep sleep and are associated with repair processes [1]. Other brain waves include theta (4-7 Hz), alpha (7-13 Hz), beta (14-30 Hz), and finally gamma (30-100 Hz), the highest frequency brain waves, which are associated with higher order cognitive processing [1]. These waves are a property of functional connectivity in the brain. Mechanistically, gamma network oscillations are generated through interneuron networks (ING) or pyramidal-interneuron networks (PING) [2]. The gamma wave is propagated through GABAergic inhibitory postsynaptic currents (IPSCs). In the inhibitory (ING) network, synchronized activity is driven by recurrent connections. Parvalbumin expressing, somatostatin expressing, and vasoactive intestinal peptide interneurons have been shown to play central roles in the modulation of gamma oscillations. Functional connections between inhibitory interneurons and excitatory pyramidal neurons drive PING network oscillations. The cholinergic system has also been shown to enable gamma oscillations [2]. The frequency of a gamma oscillation is influenced by input strength, and resonance [3].

These brain waves can be measured using electroencephalography (EEG). EEG studies have revealed that gamma waves are altered in a variety of neuropsychiatric conditions, and these alterations are thought to play a role in symptoms (cognition, mood, etc.) [2]. Therefore, it has been hypothesized that restoration of the gamma rhythms could help with symptom management. Preclinical work in rodents suggested that gamma stimulation could potentially have disease modifying effects as well [4]. Based off this work, various small clinical studies have been conducted in both cognitively normal and cognitively impaired populations [5]. Most of these pilot studies have been focused on the capacity for different types of gamma stimulation techniques to entrain gamma rhythms in the brain, but some have also explored cognitive and behavioral outcomes.

Gamma stimulation has been tested using a variety of modalities. The most commonly used approaches are sensory stimulation and electrical brain stimulation.

Non-invasive Gamma ENtrainment Using Sensory stimulation (GENUS) involves the entrainment of gamma oscillations originating in primary sensory cortices via sensory stimulation [6]. This approach was originally performed using 40 Hz light flicker to engage the visual system. Auditory stimulation was subsequently introduced, such that many studies use a combination of visual and auditory stimulation. Vibration (tactile) stimulation has also been tested to a lesser extent.

Transcranial alternating current stimulation (tACS) is a type of non-invasive electrical stimulation applied to the scalp targeting cortical brain regions, most commonly the frontal and temporal lobes [7]. It has been used in a variety of small clinical studies to entrain gamma oscillations in targeted brain networks (typically frontal-temporal-parietal).

Neuroprotective Benefit: Gamma stimulation may enhance performance on specific cognitive tasks related to the brain network engaged by stimulation, but clear impacts to global cognition or brain pathology have not been clinically observed thus far.

Types of evidence:

- 1 meta-analysis of clinical studies testing gamma audiovisual stimulation for AD
- 1 systematic review of clinical studies testing gamma audiovisual stimulation
- 1 meta-analysis of clinical studies testing 40 Hz tACS for Alzheimer's disease
- 16 clinical studies testing sensory gamma stimulation in cognitively normal populations

- 3 clinical studies testing electrical gamma stimulation in cognitively normal populations
- 7 clinical studies testing sensory gamma stimulation in Alzheimer's disease
- 6 clinical studies testing electrical gamma stimulation in Alzheimer's disease
- 1 clinical study testing sensory gamma stimulation in Parkinson's disease
- 2 clinical studies testing gamma stimulation in depression
- 1 clinical study testing electrical gamma stimulation in schizophrenia
- Several observational studies associating gamma oscillations with cognition/brain states
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

Gamma oscillations have been implicated in the coding and processing of information in the brain, particularly with respect to the integration of sensory information and higher order cognitive processing [2]. The dysregulation and dampening of these gamma waves has been observed in the context of neurological and neuropsychiatric conditions, and is thought to negatively impact sensory processing and cognitive function [2]. Consequently, it has been proposed that strengthening gamma oscillations may be a mechanism to improve the efficiency of information processing, thereby enhancing cognitive function. However, it is important to keep in mind that gamma waves occur in brain networks that can be large or small depending on the stimulus (source and strength) and the connectivity network of the neurons in which the neural activity originated [3]. As a result, there is a relationship between the method of gamma stimulation and the brain network that is entrained. As such, different types of gamma stimulation would be expected to differentially engage particular brain networks and thus have different downstream effects. This is largely what has been observed with studies of gamma stimulation to date. Strengthening of gamma oscillations in stimulus-related networks can result in minor and transient improvements to tasks engaging that brain network.
Studies to date do not support the notion that use of this technique can reliably boost overall cognitive function in cognitively normal individuals or meaningfully protect against future cognitive decline.

Most studies find that single sessions of gamma stimulation do not meaningfully impact overall cognitive function at the behavioral level [8; 9; 10; 11; 12]. The effects are transitory, such that entrainment of gamma waves does not persist for an extended duration beyond the stimulation period [10].

However, many studies find evidence of neural modulatory changes, particularly related to functional connectivity and allocation of brain resources during cognitive tasks. Additionally, there tend to be relationships between changes in functional connectivity/neural modulation and task performance.
The P3 (or P300) wave is an endogenous event-related potential associated with cognitive function, such that higher amplitudes are reflective of greater cognitive engagement and more efficient allocation of attentional resources [13]. In healthy young adults, audiovisual stimulation at 40 Hz was associated with a higher P3 amplitude and better accuracy on a working memory task [13]. The increased performance is thought to be related to the increased attention allocation, reflected by the P3 amplitude.
Blue light exposure at 40 Hz altered functional connectivity in healthy young adults, weakening it between some brain regions, and strengthening it between others [11]. While significant effects on cognition were not observed, performance on specific cognitive tasks was influenced by changes in functional connectivity strength between specific regions.
The changes in functional connectivity are reflected by changes in the power of brain waves beyond gamma entrainment. A study combining 40 Hz audiovisual stimulation with repetitive transcranial magnetic stimulation (rTMS) found that this paradigm led to reduced alpha and low-beta activity coupled with higher theta-gamma phase coupling during a recognition memory task [9].
Another study found that 40 Hz audiovisual stimulation in healthy adults led to reduced delta power and increased functional connectivity in the lower alpha band, which was associated with better performance on a working memory task [14].

There is also evidence to suggest that, in order to observe impacts to cognition, there needs to be alignment between the parameters of stimulation and specific cognitive tasks examined.
For example, auditory gamma stimulation in healthy young to middle-aged adults led to enhanced performance on some cognitive tasks (verbal), but not on others (visuospatial) [15]. This specificity may be related to congruence between the brain networks engaged by the modality (auditory) of stimulation relative to the cognitive task (auditory-verbal), as well as the level of cognitive load. Stimulation had a greater effect on performance in the context of a high cognitive load by helping to direct attentional resources, allowing for greater network efficiency.

The inability to detect significant effects on cognition in most studies, then, may stem from a combination of the lack of durability of a single session, misalignment between the task and brain networks engaged through stimulation, and the ceiling effect on cognitive performance in healthy young adults [11].

Various studies have explored methods to enhance the efficacy of gamma stimulation.

Multisensory/multimodality stimulation: Electrophysiological recordings indicate that gamma stimulation in a single sensory modality can entrain the associated primary sensory cortex, but the use of multiple modalities results in stronger entrainment which can reach/spread into deeper brain regions [16]. Scalp EEG recordings in young adults indicated that the combination of audio and visual 40 Hz stimulation resulted in higher amplitude P3 waves in the prefrontal cortex and improved working memory performance compared to audio or visual stimulation alone [13]. Synchronized 40 Hz audiovisual stimulation combined with rTMS was shown to increase task-related gamma band activity to a greater extent than rTMS alone [9]. Similarly, phase-locked 40-Hz intermittent theta-burst stimulation (iTBS) coupled with tACS resulted in more durable gamma entrainment than tACS alone [17].
Intracranial EEG recordings in patients with epilepsy have provided insight into how different stimulation parameters affect deeper brain structures. Relative to single sensory modality (visual or auditory) stimulation, multisensory stimulation resulted in the detection of more synchronized activity in electrodes located in deeper brain regions [18]. Audiovisual 40 Hz stimulation was found to be able to entrain deeper brain regions, including the gyrus rectus, amygdala, hippocampus, and insula, with the most prominent effects observed in the insula and superior temporal cortex, regions that play a role in multi-sensory integration [18].

Combination with cognitive training/engagement: Gamma oscillations are generally reflections of the engagement of particular brain networks elicited in response to stimuli and cognitive tasks. The addition of gamma stimulation can be considered a way to boost the efficacy of cognitive training. Gamma stimulation alone may not be specific or powerful enough to robustly engage networks involved in cognitive processing. Active engagement may offer more durable effects than passively receiving stimulation. For example, while gamma entrainment may be possible during sleep, it is more robust during wakefulness [19].
One study found that the combination of 40 Hz light flicker in conjunction with a cognitive task allows for a broader spread of gamma entrainment across cortical areas beyond the primary sensory (i.e. occipital) cortex [20]. The inclusion of an epilepsy patient with intracranial electrodes allowed for probing into deeper brain structures, such as the hippocampus. The addition of the cognitive task facilitated the propagation of gamma entrainment to the hippocampus, which was not observed in the context of the light flicker stimulation alone. Similarly, an intracranial EEG study in 11 patients with refractory epilepsy found that 40 Hz light flicker alone led to gamma entrainment primarily in the visual

cortex, while the combination of the 40 Hz sensory stimulation with a cognitive task resulted in increased modulation of neural activity through multiple cortical regions and the hippocampus [21].

Longer term stimulation: Preclinical models indicate neuroprotective effects from prolonged 40 Hz stimulation [6]. Due to the transience of the effects of stimulation, it appears that daily sessions over a prolonged period of time are needed for meaningful effects on brain dynamics to occur. Studies in healthy populations tend to look at acute effects, which has made it difficult to determine the threshold for the number/frequency of sessions that may be needed to have more durable effects on the brain. That benefits may emerge from more chronic stimulation is supported by a study in cognitively normal older adults (ages 55 to 85) receiving two 15-minute sessions of 20 or 40 Hz transcranial vibroacoustic stimulation per day for eight weeks [22]. The 40 Hz stimulation was associated with increased power in the gamma band, and to a lesser degree in the alpha and beta bands. This was accompanied by improvement on measures of attention, scores on the CERAD cognitive assessment, and depressive symptom scores.

Personalization/optimization of stimulation frequency: 40 Hz was selected as the optimal gamma stimulation frequency based on rodent studies, but that does not necessarily mean it is the optimal gamma frequency for humans in general, or a given individual [6; 23].
A study assessing invisible spectral flicker stimulation in healthy adults found that gamma waves could be entrained by stimulation ranging from 36 Hz to 44 Hz [24]. There was no 'optimal' frequency across the population, as there was a high degree of variability across subjects with respect to which particular frequency worked best. This leads to the concept that each individual has their own dominant gamma frequency, which generally falls between 30 Hz and 50 Hz [15], such that individuals will experience the greatest entrainment with stimulation at their individual dominant gamma frequency [25].
Aging is expected to impact an individual's dominant gamma frequency [23]. There is evidence to suggest that one's optimal gamma entrainment frequency decreases with older age. A study found that dominant gamma frequencies varied based on age and disease status [26]. Healthy young adults had the highest dominant gamma frequencies in both eyes open and eyes closed conditions, while AD patients had the lowest dominant frequencies. In the eyes open condition, the average peak gamma frequency was 37.2±1.25 Hz in healthy young (mean age: 23.9 ± 3.87) adults, 35.5±2.00 Hz in healthy older (mean age: 66.7 ± 7.69) adults, and 33.4±3.22 Hz in AD patients (mean age: 73.1 ± 6.58) [26]. Notably, in addition to shifting to lower frequencies, the distribution of dominant gamma frequencies was more variable in older adults and especially in AD patients, relative to young adults.

A clinical study in 35 cognitively normal older adults (aged ≥60) assessed visual gamma stimulation at several luminance intensities (400 cd/m^2 vs 700 cd/m^2), colors (red vs white), and gamma flicker frequencies (32 Hz, 34 Hz, 36 Hz, 38 Hz and 40 Hz) [27]. The higher luminance resulted in stronger entrainment gamma rhythms in parieto-occipital-to-frontotemporal networks. In the cohort of older participants, lower gamma frequencies (32 Hz and 34 Hz) resulted in stronger and more widespread gamma entrainment.
These studies suggest that the use of 40 Hz as the standard for gamma stimulation may be optimized for young adults, and less effective for older adults. This may also negatively impact the efficacy of this technique for dementia and other conditions where endogenous gamma waves may be altered or dampened.

Additional factors may also affect the efficacy of gamma entrainment, necessitating personalization. Many studies calibrate stimulation intensities to each participant to ensure that it is detectable but not overly aversive. This can be impacted by age-related hearing and vision loss. With respect to vision, yellowing of the lens is a common feature of aging, which can impact the reflection/absorption of different wavelengths of light [28]. The stimulation parameters and brain regions targeted will likely vary depending on which aspects of brain function one is attempting to modulate. As a result, the future of this approach may necessitate customization, such that 'off the shelf' devices with preprogrammed settings may not offer meaningful utility.

Human research to suggest benefits to patients with dementia:

The power of gamma oscillations has been shown to be reduced in individuals with mild cognitive impairment (MCI) and Alzheimer's disease (AD) [29]. It has been unclear whether the dampening of gamma waves occurs as a consequence of neuropathological changes, or if it plays an active role in the process of cognitive decline.

A variety of feasibility studies have been conducted in populations with cognitive impairment testing the capacity for gamma stimulation to both strengthen gamma waves in the brain and to improve cognitive function. The same general trends identified in cognitively healthy populations have been observed in cognitively impaired populations, such that stimulation parameters that are multidomain and long-term are associated with better gamma entrainment and outcomes. Similarly, effects on measures of brain activity and structure have been more apparent than effects on cognition. There may also be limits to the degree to which this type of stimulation can impact cognitive and functional outcomes, as a

plateauing effect has been observed. Meanwhile, the stimulation needs to be sustained over time for benefits to be maintained.

A key concern relates to the diminishing utility of this approach throughout the disease course, such that meaningful benefits may be limited to early stages when brain structure, such as white matter tracts involved in the propagation of activity across brain regions, is still largely intact [23].

Sensory Stimulation (GENUS)

The best studied to date involves multisensory audio-visual 40 Hz gamma stimulation.
A systematic review and meta-analysis including 341 participants with AD or MCI from ten RCTs and one randomized case-control study found that gamma-frequency (40 Hz) auditory and visual stimulation was associated with improvements on brain structural changes on MRI (Standardized mean difference [SMD]: 1.74, 95% CI 0.31 to 3.18), but was not associated with significant improvements to measures of cognitive function (SMD: 0.16, 95% CI -0.36 to 0.68) or activities of daily living (SMD: 0.53, 95% CI -1.26 to 2.33) [30]. This calls into question whether the observed changes to brain structure, plasticity, and efficiency can meaningfully impact clinical outcomes.

The most extensive study completed to date has been the randomized, double blind, sham-controlled, Phase 2a OVERTURE clinical trial (NCT03556280) in 76 patients with mild to moderate AD (MMSE 14 and 26; aged ≥50 years old) [31]. Participants were randomized to six months of audio and visual stimulation using Cognito Therapeutic's Evoked Gamma Therapy System (CogTx-001; Spectris™) administered one hour per day at a frequency of 40 Hz (gamma stimulation) or sham conditions. Following in-clinic parameter optimization, sessions were performed at home with the assistance of a caregiver. The study was powered for safety rather than clinical outcomes. No significant differences were observed on the primary cognitive outcome of the Mild/Moderate Alzheimer's Disease Composite Score (MADCOMS) (Change in least squares mean [ΔLSM]: -0.23, 95% CI -1.38 to 0.91), or the secondary cognitive outcome measures of Clinical Dementia Rating - Sum of Boxes (CDR-SB) (ΔLSM: -0.06, 95% CI -0.93 to 0.82) or the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog14) (ΔLSM: 1.51, 95% CI -2.13 to 5.15) [31]. While nominally significant improvements were observed on exploratory cognitive measures of the Mini-Mental State Examination (MMSE) and Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL) total score, no significant effects were observed on the ADCOMS, neuropsychiatric inventory (NPI), quality of life, Zarit Scale of Caregiver Burden/Zarit Burden Interview (ZBI), or the integrated Alzheimer's Disease Rating Scale (iADRS).

An analysis of 22 participants from this study did find a potential beneficial effect on daily rhythms [32]. The weakening of circadian rhythms is a common feature of AD, resulting in the disruption of typical 24-activity patterns. During the first 12 weeks of treatment, participants receiving active gamma stimulation exhibited a lower degree of nighttime activity relative to those receiving sham stimulation, though this difference weakened over time.

While robust changes to cognition or behavior were not observed, structural brain changes were detected on MRI, particularly within the white matter, suggestive of a strengthening of functional networks. The degree of whole brain volume loss was reduced by 69% in the active group, with effects particularly pronounced in the occipital cortex (involved in visual processing), but there were no significant effects on hippocampal volume [31]. In a subset of 50 participants, the area of the major white matter tract connecting the two brain hemispheres, the corpus callosum, was larger in those receiving active gamma stimulation for six months (+2.28 ± 0.87%) [33]. The effect was observed at three months, and was more pronounced at six months, suggesting a slowing of white matter atrophy. Similarly, in a subset of 38 participants, total white matter volume was found to be higher in those receiving active stimulation, due to a loss of volume in those receiving sham (+0.17±1.08% vs. -2.54±1.38%) [34]. The effects were observed in a variety of brain regions, including the entorhinal cortex, which is a critical hub connecting the hippocampus and cortex that is affected in AD.

The Cognito Spectris™ gamma stimulation device is currently being tested in a pivotal randomized, double-blind, sham-controlled, clinical trial in over 600 patients with mild-to-moderate AD (NCT05637801).

A separate single-blind, randomized, placebo-controlled Phase 2a trial (NCT04055376) tested audio and visual gamma stimulation at 40 Hz or control stimulation (constant light and white noise) in 15 patients with probable mild AD for one hour per day for six months [18]. The visual stimulation was delivered via a white light LED panel (intensity 390–400 lux), while the audio stimulation was delivered via a speaker sound system (loudness 68 dB). The results were similar to the OVERTURE trial in that modest improvements on daily behavioral rhythms and brain connectivity with gamma stimulation were not accompanied by significant impacts to overall cognitive function over the course of the study duration. By three months, active participants experienced a stabilization of ventricular volume and hippocampal volume on structural MRI, while those in the control group experienced further ventricular enlargement and hippocampal atrophy [18]. But there were no changes in total brain volume or cortical thickness. Functional MRI indicated an increase in mean functional connectivity between the medial visual network and other brain regions in the active group, including increased connectivity between the

hippocampus and visual cortex. Actigraphy recordings indicated that the active group exhibited a modest improvement in the coupling of daily activity patterns to environmental cues [18].
There were no significant effects on cognitive performance on the MMSE, ADAS-Cog, CDR-Rating, or Montreal Cognitive Assessment (MoCA). Increased accuracy specifically on the face-name association delayed recall test (FNA-DRT) was associated with increased functional connectivity in the medial visual network [18].
This is consistent with what is observed in cognitively healthy populations, such that impacts to cognitive function are typically only detectable on tasks that specifically engage the brain networks readily activated by the stimulation paradigm, such as the visual cortex in the case of visual stimulation.

An open-label extension of this study (NCT04055376) including five participants who continued the daily 40 Hz audio and visual stimulation paradigm for over two years found that efficacy varied in participants with late-onset AD (n=3) relative those with early-onset AD (n=2) [35]. Similar to what was observed in the primary trial, the brain response to gamma stimulation was most pronounced in the occipital (visual) brain network. While gamma rhythm entrainment was robust in participants with late-onset AD, it weakened over time in those with early-onset AD. This was coupled with stabilization of cognitive function (on MMSE, CDR-SOB, and Functional Assessment Scale [FAS]) relative to historical controls in participants with late-onset AD, but continued cognitive decline was observed in those with early-onset AD.

A case-series including three patients with MCI or AD assessed the impact of a year of tactile vibration and auditory 40 Hz gamma stimulation administered via a vibroacoustic chair device on cognition and mood [36]. With caregiver assistance, the patients used the chair five times per week for 30 minutes per day. The participants generally had a positive experience, demonstrating improvements in mood and stabilization of cognitive function.

With long-term use, patients in relatively early stages of disease may achieve some stabilization of cognitive function due to the strengthening of brain network efficiency. However, durability is unclear and may be dependent on individual patients' disease trajectories. The modest effects of gamma stimulation may not be noticeable in rapid progressors. Additionally, the ability of this technique to influence brain networks may diminish over time due to ongoing neurodegeneration.

Overall, these studies suggest that the ability to impact cognitive function is dependent on the degree to which the stimulation paradigm engages particular brain networks. With the strengthening of gamma

entrainment in specific brain networks, performance on tasks which rely on those networks can be improved. However, this may not extend to other brain networks, or cognition more generally. Consequently, functional and structural changes observed on MRI tend to correlate with performance on specific tasks, but not with general cognition batteries. These changes may not be robust or widespread enough to meaningfully alter cognitive trajectories. The engagement of single sensory modalities is likely to be insufficient to have clinically meaningful effects, as it is necessary for the stimulation to impact deeper brain structures involved in information integration and processing.

Electrical Stimulation

The use of more intensive electrical stimulation paradigms (i.e. tACS, TMS) with the capacity to more reliably engage deeper brain networks is an alternative approach that has been tested in a variety of proof-of-concept studies.

A meta-analysis of seven studies with a total of 159 participants, including three RCTs, three clinical trials, and one case series, testing 40 Hz gamma stimulation administered by tACS found that effects on cognition varied depending on the brain regions targeted by the stimulation [37]. Overall, 40 Hz tACS was associated with improvements on overall cognition (SMD: 0.49, 95% CI 0.09 to 0.89) and memory (SMD: 0.79, 95% CI 0.18 to 1.41). Subgroup analysis indicated that stimulation targeting the temporo-frontal or bilateral temporal lobes improved overall cognitive performance, while targeting the left angular gyrus improved memory. Effects were less robust in a home use setting, which could be related to less precise targeting.

An open-label trial (NCT04646499) testing 40 Hz tACS in 13 patients with amnestic MCI found that stimulation-related changes in functional connectivity were associated with performance on specific cognitive tasks [38]. The participants received eight one-hour sessions of tACS targeting brain regions involved in episodic memory processing administered over the course of four weeks. Changes in resting state functional connectivity were associated with white matter tract integrity and hippocampal excitability. Episodic memory performance improved in participants experiencing the greatest degree of tACS-induced electrical stimulation in relevant brain regions and the greatest changes in functional connectivity. This suggests that efficacy of this technique depends on the relative integrity of the targeted white matter brain network.

Two open-label studies (NCT03290326; NCT03412604) including a total of 15 patients with mild to moderate AD tested the effect of 40 Hz gamma stimulation tACS targeting the temporal lobe,

administered for one hour per day for two or four weeks on cerebral blood flow and cognition [39]. Gamma spectral power changes were associated with increased blood perfusion in the temporal lobe. While there were no significant effects on global cognition, increased cerebral blood flow was associated with better performance on specific cognitive tasks related to episodic memory and fluency.

A double-blind, randomized, sham-controlled clinical trial (NCT05643326) tested a home-based gamma tACS system in 50 patients with prodromal and mild AD. Participants received tACS for one hour per day, five days per week for eight weeks [40]. Marginal mean differences were observed in cognitive performance on the CDR-SB, ADAS-Cog, and ADCS-ADL between the active and sham groups. The study also included an additional eight-week open-label phase. Cognitive benefits plateaued following a single eight-week course, suggesting a ceiling/limit to the amount of improvement that can be achieved with this technique.

Similar to what has been observed in cognitively healthy populations, the addition of cognitive training in conjunction with gamma stimulation may allow for greater propagation of effects through deeper brain networks, resulting in more pronounced and durable effects.
A randomized, crossover, double-blind, sham-controlled trial including 42 dementia patients tested the effect of 40 Hz tACS gamma stimulation applied to the left dorsolateral prefrontal cortex (dlPFC) and contralateral supraorbital area combined with simultaneous cognitive exercises on cognition and neuropsychiatric symptoms [41]. The left dlPFC was selected due to its central role in the default mode network, important for complex cognitive processing. The protocol consisted of two 30-minute tACS sessions per day, five times per week for four weeks, coupled with cognitive exercises using the MindTriggers app. Improvements in neuropsychiatric symptoms were observed with both active and sham stimulation. Notably, cognitive scores on the ADAS-Cog improved with gamma stimulation but not with sham stimulation, with improvements sustained up to two to three months.

Preclinical studies suggest that in addition to cognitive effects related to changes in brain network activity, gamma stimulation, specifically, may also have a disease modifying effect by reducing the accumulation of pathological proteins in the brain [4]. However, these effects have not been translated to meaningful changes in biomarkers of AD pathology in clinical studies to date [1; 16]. It is unclear the degree to which gamma stimulation can impact brain pathology in human patients. The lack of effect could be related to differences in the relative intensity of 40 Hz stimulation used in clinical studies compared to what has been done in animal studies, resulting in less durable impacts to deep brain regions and overall function.

A clinical study including six AD patients with PET confirmed Aβ found that 40 Hz light flicker administered two times per day for 10 days did not significantly alter brain Aβ levels based on Aβ PET imaging [42]. Similarly, treatment with 40 Hz audiovisual stimulation for six months did not significantly impact Aβ levels based on PET imaging in the OVERTURE trial [31].
In an open-label extension study including 5 participants testing audiovisual 40 Hz stimulation for over two years, reductions were seen in plasma ptau217 of 47% and 19%, respectively, in two participants with late-onset AD who had also experienced cognitive stabilization [35]. However, without controls or comparisons with the other participants who continued to decline, these results are difficult to interpret.

Clear effects on AD biomarkers have also not been observed in the context of gamma tACS stimulation. An open-label 40 Hz tACS study in 13 patients with amnestic MCI did not detect changes on plasma AD biomarkers, including Aβ42, Aβ40, ptau181, NFL and GFAP, following four weeks of treatment [38]. Similarly, a study testing home-based gamma tACS in 50 patients with prodromal or mild AD for eight weeks did not observe significant changes on plasma AD biomarkers (Aβ42, Aβ 40, NFL, GFAP, and ptau217) [40].

A key concern with many of the gamma stimulation approaches is long-term tolerability, since benefits from this approach require long-term consistent use. Electrical stimulation can lead to physical discomfort, while aversive sensory stimulation can result in less attentional engagement, and thus less robust entrainment [43]. A variety of approaches have been proposed to improve tolerability, some of which have been tested in proof-of-concept studies.

Transcranial magnetic stimulation (TMS) creates an electric field in the brain using electromagnetic induction, which typically use high intensity magnetic fields (~1 tesla) (see Transcranial Magnetic Stimulation report) [44]. Since this may not be feasible for chronic use, studies have been testing the effect of lower intensity TMS. A randomized, double-blind, sham-controlled, crossover pilot study tested the effects of a single (40 minute) session of low intensity gamma TMS (gTMS) targeted to the precuneus in 21 patients with probable mild AD dementia [44]. The low intensity gTMS was able to entrain gamma rhythms in frontal brain regions, though the effect was transitory. While there were no significant effects on cognition, there were correlations between frontal gamma entrainment and performance on specific cognitive tasks, similar to what is observed with other gamma stimulation modalities.

Invisible spectral flicker/Multi-luminaire: One method to improve the experience of light flicker is to reduce the conscious detection of the light by using a technique called invisible spectral flicker [45]. It involves the alteration of two waves of similar color temperature that are spectrally distinct. A study in healthy participants found that compared to traditional 40 Hz light flicker, 40 Hz ISF evoked weaker electric potentials in the visual cortex, but had better tolerability [46]. A randomized, placebo-controlled, double-blinded, pilot study (NCT04574921) including 11 patients with mild-to-moderate AD tested the effect of invisible spectral flicker for one hour per day for six weeks [47]. There were no significant effects on brain morphology or cognition, though there was a high degree of variation across participants. Invisible spectral flicker is currently being tested in the randomized, double-blinded, placebo-controlled ALZLIGHT clinical trial (NCT05260177) in patients with mild-to-moderate AD [45]. Another technique called multi-luminaire combines weak 40 Hz stimulation with strong non-flicker light from an adjacent light source to mask the flickering effect, and reduce discomfort [48]. One non-randomized case-control study found that use of 40 Hz multi-luminaire for 12 weeks had some modest benefits on measures of mood and cognition [49], while a separate clinical study found that 40 Hz multi-luminaire did not reliably elicit gamma oscillations based on EEG measures [50]. Both studies utilized the same multi-luminaire device.
Some researchers have expressed skepticism regarding these approaches, suggesting that the degree of entrainment that could be achieved may be below the threshold of biological meaningfulness [48].

Gamma music: A randomized cross-over trial in older adults with MCI assessed the acceptability of auditory stimulation delivered as self-selected music, 40 Hz pure tones, and 40 Hz music (customized music playlists integrated with a 40 Hz soundtrack) one hour per day/five days per week for four weeks [51]. Interviews with 25 participants indicated varying degrees of acceptability across the conditions. Around half of the participants who experienced the 40 Hz pure tone reported that it was aversive, with a subset experiencing tinnitus. The acceptability of the approach was improved by integrating the 40 Hz with music. The differential impact of these approaches on gamma entrainment in the auditory cortex (or other brain regions) was not assessed. A separate study in healthy older adults, also found that the gamma music approach was generally well-received and well-tolerated by participants [52].

Transcranial photobiomodulation involves the use of near-infrared light to activate photosensitive reactive centers in enzymes/molecules involved in cellular function (see Photobiomodulation report) [53]. While the majority of studies use continuous wave light, some studies have found that the use of pulsed light may allow for deeper brain penetration [53]. Using EEG analysis, some pilot studies have shown that when pulsed at a frequency of 40 Hz, this technique may also entrain gamma rhythms [54;

55]. It has not been established how it compares to other approaches, but, in general, transcranial photobiomodulation tends to suffer from many of the same limitations as sensory stimulation, including limited ability to modulate deep brain structures and limited durability [53].

Transcutaneous auricular vagus nerve stimulation (taVNS) is a form of non-invasive vagal nerve stimulation in which the electrodes are placed on the ear to stimulate the auricular branch of the vagal nerve (see Vagal Nerve Stimulation report). One study in 80 healthy right-handed young adults found that a 30-minute session of 40 Hz taVNS led to gamma entrainment in brain regions involved in attention and inhibitory control [56]. This was accompanied by improved performance on a working memory task.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Parkinson's disease: POTENTIAL MODEST MOTOR BENEFIT
Motor activity has been shown to be associated with the modulation of neural oscillations in several frequency bands [57]. Gamma waves have been described as prokinetic due to their association with voluntary movement characteristics, and play roles during both motor planning and execution. As a result, the modulation of gamma activity has been suggested as a possible therapeutic intervention to facilitate motor rehabilitation.
A randomized, double-blind, controlled study in 25 patients with Parkinson's disease tested the impact of 30 minutes of gamma frequency (35 Hz) acoustic binaural beat stimulation in comparison with conventional acoustic stimulation on motor performance alone or in conjunction with dopaminergic mediation conditions [58]. In the presence of dopaminergic medication, motor symptoms were not improved with either type of acoustic stimulation. In the absence of dopaminergic medication, an improvement in resting tremor was observed in the more affected limb with gamma stimulation, but there was no improvement in overall motor symptoms.
The optimal modality of gamma stimulation to activate/regulate disease-relevant motor networks has not been established. It may vary from person to person depending on their motor symptoms and pattern of disease progression. A variety of clinical studies are ongoing testing different modalities of gamma stimulation, including visual stimulation, audiovisual stimulation, and tACS stimulation targeting the motor cortex.

Stroke: POTENTIAL BENEFIT FOR REHABILITATION (preclinical)
Due to purported roles in the regulation of both cognitive and motor function, gamma stimulation has been proposed as a therapeutic intervention to both facilitate motor rehabilitation and mitigate post-stroke cognitive impairment. Studies have found a weakening of low gamma (30 to 50 Hz) oscillations emanating from the lesion to the peri-infarct area, indicating an inability for neural activity to effectively propagate through brain networks including the lesioned area [6].
As a proof-of-principle, optogenetic stimulation of interneurons at a frequency of 40 Hz administered during the acute phase in a rodent stroke model reduced neurological deficits, which was accompanied by an improvement in functional synaptic plasticity and downregulation of cell death pathways in the brain [59]. Another study found that optogenetic gamma stimulation of parvalbumin interneurons in conjunction with motor training during the subacute phase facilitated motor improvements in forelimb function in a rodent stroke model [60]. A key challenge is being able to specifically target the brain networks impacted by the stroke lesion in a clinical setting. As a translational proof-of-concept, this study also tested the impact of 40 Hz tACS applied over the perilesional area of the premotor cortex in conjunction with motor rehabilitation, and found that this method also facilitated motor recovery and led to an improvement in limb function [60]. Rather than restore pre-lesioned network activity, this approach appears to facilitate compensatory network reorganization.
There are likely to be additional translational challenges, such as determining the optimal window for intervention, and the fact that lesion areas will vary from patient to patient, such that some may be more amenable to targeting from transcranial stimulation approaches, whereas other locations may be challenging to target. There are several active clinical studies testing the ability of sensory [61] and tACS [62] gamma stimulation to enhance motor recovery following stroke.

Schizophrenia: POTENTIAL BENEFIT FOR HALLUCINATIONS
Several studies have found that gamma oscillations are altered in patients with schizophrenia, particularly in response to auditory stimuli [63]. This altered left frontotemporal network activity is thought to contribute to auditory hallucinations. Therefore, normalization of auditory-related gamma oscillations in this network has been proposed as an intervention to mitigate auditory hallucinations.
An RCT including 32 schizophrenia patients with refractory auditory hallucinations tested the impact of 20 sessions of 20-minute daily gamma (40 Hz) tACS stimulation on functional connectivity [64]. The stimulation was applied to the dlPFC and left temporoparietal junction, thereby engaging frontal-temporal-parietal networks. Participants continued to take their prescribed antipsychotic medications throughout the study. The 40 Hz tACS stimulation increased functional connectivity in the low gamma band frequency. It also impacted network controllability, or the ability of activity in particular brain

regions to drive the network into a particular state [65]. Highly connected brain hubs exert the most control over the network. These changes in controllability in the frontal lobe may facilitate the normalization of auditory processing. Participants receiving 40 Hz tACS reported a lower burden of auditory hallucinations at the end of the study, which may have been related to changes in network activity [64].
The impact of sensory gamma stimulation is currently being tested in clinical studies.

Depression: POTENTIAL BENEFIT FOR COGNITIVE SYMPTOMS
Gamma rhythms have been shown to be altered in the context of depression, particularly in brain regions implicated in emotional regulation and mood. Gamma stimulation may also be beneficial for alleviating depression-related cognitive impairment.
A pilot RCT (NCT02339285) including 32 patients with major depressive disorder tested the impact of tACS administered to frontal brain regions for 40 minutes per day for five days at frequency of 10 Hz or 40 Hz [66]. There were no significant differences in depressive symptoms at the end of the study, but exploratory analysis suggested that 10 Hz stimulation was associated with better response rates.
A clinical study including 141 patients with clinical depression tested the effect of adding audiovisual gamma sensory stimulation coupled with a working memory cognitive task administered via a mobile app for 28 days to standard antidepressant therapy [67]. This stimulation-training paradigm was associated with improved cognitive function in those exhibiting cognitive impairments at baseline, but did not significantly impact depressive symptoms.
These studies suggest that different stimulation strategies are likely needed to target the emotional and cognitive symptoms of depression, due to the differential impact of different brain networks mediating these phenotypes. Further work is needed to determine optimal stimulation paradigms. Additional clinical studies testing gamma stimulation for depression are ongoing [68].

Animal studies
The ability of 40 Hz stimulation to modify brain pathology and function was first uncovered through rodent models [1; 4]. These studies have provided insight into the mechanisms of neuroprotection as well as limitations to the approach and methods to boost efficacy.

The majority of the studies have been conducted in rodents. Due to differences in brain size and architecture, the translatability of these stimulation approaches to humans is difficult to determine. One study conducted in non-human primates lends support to the translatability of the approach. Nine aged rhesus monkeys (26 to 31 years old) received 40 Hz auditory stimulation for one hour per day (starting

at 10 am) for seven days [69]. Biomarker analysis indicated levels of Aβ42 and Aβ40 in the CSF increased by two-fold in response to gamma stimulation, whereas random stimulation did not impact CSF Aβ levels. CSF levels of total tau or ptau-181 were not significantly altered, but postmortem tissue analysis indicated that the monkeys did not have meaningful levels of tau accumulation in the temporal cortex.

Mechanisms:

Induction of neurotrophic factors/neurogenesis: Gamma stimulation may play a role in activity-dependent neural plasticity [70]. The enhancement of GABAergic transmission from parvalbumin interneurons in response to gamma stimulation supports adult neurogenesis [71]. Intracranial alternating current stimulation (iACS) at a 40 Hz frequency promoted neurogenesis in the subventricular zone (SVZ) and to a less extent in the hippocampus in mice [72]. Whether these effects could be translated to humans in the context of tACS is unclear. The maximum current density and electric field magnitude used in this study were around 100 times higher than human transcranial stimulation. Additionally, current applied at the scalp largely shunts outside of the brain. Current distributing to the CSF may allow for electrical clustering at the SVZ, but further optimization would be needed.

Sensory gamma stimulation has also been shown to enhance neurogenesis in mice [70]. Effects on neuronal plasticity were dependent on the stimulation conditions including the duration and number of sensory domains involved. More robust effects were observed with longer duration (>1 hour) and multisensory (audio and visual) stimulation [70]. Clinical human studies, however, typically use stimulation durations ≤1 hour, suggesting that these plasticity benefits may not be achievable with currently used parameters.

The induction of this activity-dependent plasticity has been shown to involve neurotrophin signaling, particularly the TrkB receptor [70]. TrkB signaling in interneurons is critical for gamma band synchronization across brain networks [71]. TrkB serves as a receptor for brain-derived neurotrophic factor (BDNF), which plays an important role in synaptic plasticity. The modulation of neuronal excitability in response to gamma stimulation has been shown to be dependent on TrkB signaling [71]. Knocking down the TrkB receptor blocked the modulation of interneuron excitability/gamma entrainment in mice. Since reduced TrkB activity has been observed in the context of AD, the efficacy of gamma stimulation may be negatively impacted [71]. This may contribute to the decline in gamma entrainment observed with progression into later stages of disease. This suggests that this stimulation technique may be more effective when paired with a TrkB agonist [71].

Neuroimmune modulation: Sensory 40 Hz gamma stimulation has been shown to affect neuroimmune signaling, which impacts the trafficking and function of microglia [16]. In mice, light flicker impacted

cytokine expression in the visual cortex in a frequency dependent manner [73]. Many of the cytokines induced by 40 Hz stimulation are associated with neuroprotective functions [73].

Glymphatic clearance: Multi-sensory gamma stimulation has been shown to potentiate glymphatic clearance in mouse models [74]. Interneurons can regulate glymphatic clearance via the modulation of arterial pulsatility in an aquaporin-4 dependent manner [74]. This appears to stem from the activation of adrenergic adenosine-A2A receptor (A2AR) signaling in response to the activity-dependent release of adenosine [75]. The enhancement of the glymphatic system may then facilitate the clearance of pathological proteins, such as amyloid. It has not yet been established whether and under which conditions 40 Hz stimulation can induce a similar effect in humans.

Strengthening of circadian rhythms: The weakening of 24-hour circadian rhythms is a common feature of AD [76]. The central clock located in the hypothalamus, the suprachiasmatic nucleus (SCN), can be entrained by external cues, particularly sunlight via specialized cells (intrinsically photosensitive retinal ganglion cells) in our eyes, which are especially sensitive to blue light. In mice, blue light (462.8 nm) flicker at a frequency of 40 Hz administered one hour per day for 30 days enhanced the rhythmicity of neuronal inhibitory currents in the SCN in an AD model [77]. This was accompanied by more robust expression of central clock genes (e.g. Bmal1, Clock, and Per2) and improved circadian behavioral patterns. The light flicker was administered near the start of the natural light phase (i.e. morning) when sunlight is most enriched in blue light wavelengths. The timing and light color may be important features of strengthening circadian rhythms. In clinical use, it may be important to conduct light flicker stimulation at the same time each day, such that both the wavelength and time of day could influence behavioral outcomes. Modest impacts on daily activity patterns, which could be indicative of a strengthened circadian clock have been observed in a couple clinical studies using white LED lights [18; 32]. In the OVERTURE trial, participants were instructed to use the device (audio and visual stimulation) during the morning hours [31]. It is unclear the degree to which this protocol could be optimized to further strengthen molecular and behavioral rhythms, or if there is a limit to the degree of benefit related to the extent of neurodegeneration.

Combination with exercise training: The neuroprotective benefits of gamma stimulation alone appear to be relatively weak, but combining it with other interventions may boost the durability of the effects. The combination of a 12-week exercise regimen with 40 Hz light flicker stimulation improved cognitive function in the 3xTg AD mouse model at both early (5 months) and late (12 months) stages [78; 79]. The combination treatment more effectively induced neurotrophin expression (BDNF), and synaptic protein

expression in the hippocampus than either treatment alone [78; 79]. Additionally, the combination resulted in a greater reduction in proinflammatory cytokine induction and more robust effects on biomarkers associated with improved mitochondrial function. The combination also most effectively improved insulin signaling in the hippocampus, which was associated with enhanced cell differentiation [80]. This combination has not yet been tested in human clinical studies, such that a protocol that would optimize synergism between these interventions has not yet been established.

Challenges:

Lack of consistency across studies: The greatest challenge associated with gamma stimulation stems from the way in which changes to stimulation parameters can influence outcomes, resulting in a lack of consistency across preclinical studies. One study found that acute (1 hour) 40 Hz visual stimulation did not impact Aβ load in the APP/PS1 or 5XFAD mouse models [43]. Stimulation for one hour per day for seven days did not reliably entrain gamma oscillations, impact microglia recruitment, or Aβ load within the hippocampus in 28-week-old 5XFAD [43]. Notably, in the original study, these parameters were impacted in the hippocampus in response to optogenetic 40 Hz stimulation targeted to the hippocampus, while light flicker only impacted these measures within the visual cortex [4]. Another study in 5XFAD mice found that stimulation with 40 Hz light flicker for one hour per day for five weeks starting at four months of age did not impact microglial morphology or Aβ load in either the visual cortex or hippocampus [81]. The discrepancy could be related to different ages/disease stages, as the original study tested an earlier stage (3 months of age), which may have been more likely to respond [28].

Furthermore, a separate study in 5XFAD mice found that sensory stimulation differentially affects gene expression depending on the brain region, stimulation frequency, and duration [82]. Audiovisual stimulation at 10, 20 or 40 Hz was found to activate genes associated with neuroimmune responses and synaptic plasticity within the visual cortex [82]. Meanwhile, gene expression induced in the hippocampus varied depending on the stimulation frequency. Transcriptional changes were also affected by the duration of stimulation. A study on neuroimmune responses has also shown that expression of immune-related signaling pathways, such as NF-kB and MAPK, varies in a duration-dependent manner [73]. Together, these studies indicate that stimulation parameters may need to be fine-tuned to elicit specific effects in a given brain region, necessitating personalized, rather than standardized, parameters.

These rodent studies are consistent with clinical studies indicating that sensory stimulation alone tends to impact only sensory cortices/networks, and that stimulation targeting deeper structures or combined

with other interventions (e.g. cognitive training/additional modalities) are needed to reach disease-associated brain regions/networks. They further highlight that efficacy is likely impacted by the stage of disease, and that small changes in stimulation parameters can differentially impact outcomes.

Sex Effect: Preclinical studies suggest that sex may impact differential transcriptional and behavioral responses to stimulation at different frequencies. In two- to three-month-old mice, audiovisual stimulation for one hour per day affected stress-related, behavioral, glial, and synaptic measures in a sex and frequency dependent manner [83]. Male mice experienced mitigation of stress and anxiety-like behaviors following 10 Hz stimulation, which was associated with altered gene expression in related pathways. For female mice, 40 Hz stimulation more effectively mitigated stress-related behavioral and transcriptional changes. In general, 40 Hz stimulation modulated a broader array of genes, while 10 Hz led to a more targeted response to stress-related genes. Meanwhile, a study utilizing tACS stimulation in four-month-old mice found that 40 Hz stimulation targeted to the left PFC enhanced spatial memory in males, while females responded to both 10 Hz and 40 Hz stimulation [84].
Clear sex differences have not been detected in clinical gamma stimulation studies to date. However, this may be related to the lack of robust behavioral effects, and that analysis of brain biochemical/transcriptional effects is not feasible in living humans and thus not performed.

APOE4 interactions: It has not yet been established whether the efficacy of gamma entrainment using stimulation approaches or cognitive outcomes are influenced by ApoE4 status. There is some evidence to indicate that slow gamma oscillations are attenuated in hippocampal networks in the presence of ApoE4 [85].

Aging and related health concerns: Gamma wave stimulation is directed toward modulation of brain function and used primarily for neurological conditions.

Types of evidence:

- 1 review of gamma waves in pain processing
- 2 clinical trials on stimulation in neuropathic pain

Neuropathic pain: GAMMA WAVES MAY BE A BIOMARKER OF PAIN PERCEPTION
Gamma band oscillations may serve as biomarkers of pain perception [86]. The amplitude of the oscillations is associated with perceived pain intensity by a given individual. These oscillations appear to

be involved in pain processing. Therefore, targeting these gamma band oscillations has been proposed as a therapeutic approach for pain management. A variety of different stimulation techniques have been tested which show promise for gamma wave modulation and analgesic effects.

Dorsal root ganglion stimulation (DRG-S) is used for the treatment of chronic pain and involves the implantation of a stimulation device implanted in the spinal column in which the electrodes target the dorsal root ganglia that allows for more targeted pain relief compared to a more generalized approach with spinal cord stimulators [87]. A study including nine patients with unilateral, localized neuropathic pain receiving DRG-S found that following seven days of stimulation, pain scores were reduced by an average of 70%, which was associated with a reduction in resting-state gamma power (30-45 Hz range) specifically on the side of the brain biologically relevant to the pain affected region [88].
Another study including 19 patients with chronic neuropathic pain implanted with a DRG-S system found that the frequency of DRG-S may impact the degree of pain control. Compared to their regular use of 20 Hz stimulation, higher frequencies in the gamma range (40-80 Hz) were associated with less pain relief [89].
The frequency/stimulation parameters that provide the best relief may vary based on the condition and type of stimulator. There are a variety of clinical trials testing spinal cord stimulation parameters in the gamma range.

Safety: Gamma stimulation is generally safe and well-tolerated. Sensory stimulation may induce tinnitus, headache, fatigue, and eyestrain. Electrical stimulation may induce temporary burning/stinging at stimulation sites, headache, and visual disturbances.

Types of evidence:

- 1 meta-analysis of clinical studies testing gamma audiovisual stimulation for AD
- 1 systematic review of clinical studies testing gamma audiovisual stimulation
- 1 meta-analysis of clinical studies testing 40 Hz tACS for Alzheimer's disease
- 1 review of gamma tACS
- 2 reviews of sensory gamma stimulation
- 4 clinical studies testing sensory gamma stimulation
- 6 clinical studies testing electrical gamma stimulation
- Numerous laboratory studies

GENUS

Gamma sensory stimulation has generally been shown to be safe and well-tolerated across studies.
A systematic review including 62 studies testing sensory gamma stimulation found that adverse events were generally mild, with headache, dizziness, and tinnitus as the most commonly reported events [23].
A systematic review and meta-analysis including 11 studies testing audiovisual gamma stimulation found that this technique was not associated with an increase in overall adverse events, but was associated with an increased risk for tinnitus (RR: 6.46) [30].
The propensity for adverse events is likely related to a combination of the stimulation conditions, such as intensity, as well as individual sensitivities. With respect to light flicker, moderate intensity light (400 cd/m^2) is generally recommended as a compromise between safety and efficacy [5]. While higher intensity light can more effectively entrain gamma rhythms, it carries a higher risk for adverse events, including fatigue, dizziness, and eye pain [5]. Light flicker may also pose a risk to individuals with photosensitive epilepsy [6].

Audiovisual gamma stimulation for six months was generally well tolerated in AD patients in the OVERTURE trial. Adverse events that occurred more frequently with active stimulation were tinnitus (15%) and headache (22%) [31].
Long term daily use (2+ years) was not associated with adverse events in a small (n=5) open-label extension study of audiovisual gamma stimulation in AD patients [35].

In an eight-week study, transcranial gamma vibroacoustic stimulation was associated with a low percentage (13%) of mild adverse events in older adults, including headache, dizziness, and device discomfort [22].

A pilot trial testing invisible spectral flicker for six weeks found that adverse events were mild and uncommon, with possible treatment-related events of fatigue and eyestrain [47].

Electrical stimulation

tACS: A meta-analysis of seven studies testing 40 Hz tACS found that transient side effects included tingling, scalp irritation, visual alterations, and headache [37]. This is consistent with overall safety profile of tACS as a therapeutic modality [90].
A separate review of gamma frequency tACS studies found that the technique was generally well tolerated, with only modest and temporary side effects reported, including headache, nausea, fatigue, and skin reactions (at electrode site) [7]. The authors note that it is important to consider individual

differences in brain anatomy and electrical conductivity in determining electrode placement and stimulation intensity to minimize risks.
In two open-label studies testing 40 Hz tACS in 15 patients with mild to moderate AD for two to four weeks, reported mild side effects included tingling, scalp irritation, visual changes, and headache [39]. In another four-week gamma tACS open-label study in 13 patients with MCI, the ratings for common tACS-related side effects were extremely low, close to undetectable [38]. In an eight-week home-based gamma tACS study in 50 patients with prodromal or mild AD, adherence was high and use of the technique was rated low in terms of caregiver burden [40]. The primary side effect was visual phenomena.
In a proof-of-concept study in 30 healthy young adults, the addition of phase-locked gamma tACS to intermittent theta-burst stimulation (iTBS) increased the incidence of visual phenomena, but did not impact the incidence of other stimulation-related side effects [17].

TMS: Low intensity gamma TMS was found to be well-tolerated in a pilot study [44]. The most common side effect was headache in both the active and sham conditions.

taVNS: Reported side effects included transient mild stinging and burning sensations, which resolved within 30 minutes poststimulation [56].

Drug interactions: Interactions are not well-established. The cholinergic system and the GABAergic system are involved in the generation and modulation of gamma waves [2], such that drugs that modulate these neurotransmitter pathways may impact the efficacy and safety of gamma entrainment techniques.

Sources and dosing:

Gamma (40 Hz) stimulation has not yet been approved for the treatment of any neurological condition. Numerous companies have direct-to-consumer products marketed as gamma stimulation devices.
The most clinically advanced device is the Spectris™ audiovisual gamma stimulation device from Cognito Therapeutics, which has received FDA Breakthrough Device Designation for the treatment of cognitive and functional symptoms in AD, and is currently being tested in the HOPE study including over 600 patients with mild-to-moderate AD.

Clinically effective dosing has not yet been established, and may depend on the patient population, brain areas targeted, and type of symptoms that are targeted. In general, consistent use is needed for the maintenance of benefits. The most common stimulation paradigm is 40 Hz stimulation administered for one hour per day. Some studies suggest that with respect to visual stimulation, it is best if it is administered in the morning, around the same time each day, as this may also boost circadian rhythm networks [77]. It is unclear whether similar time-of-day effects are relevant for other modalities of stimulation. The use of 40 Hz is unlikely to be the optimal gamma stimulation frequency for most adults, particularly older adults, for which gamma frequencies in the low-to-mid thirties may more robustly entrain gamma rhythms [27]. The dominant/optimal gamma frequency varies from person to person [25], thus EEG analysis may be needed to accurately determine the best frequency for gamma stimulation for a given individual.

Research underway:

There are numerous active clinical trials testing different forms of gamma stimulation using a variety of different modalities. Unless otherwise specified, most studies are testing gamma stimulation for the capacity to improve cognitive function.

Sensory:

Light Flicker approaches are being tested in trials for:
Alzheimer's disease/MCI: NCT05260177; NCT07318038
Parkinson's disease: NCT07323121 (for insomnia)
Cognitively normal older adults: NCT06715995
Schizophrenia: NCT06907420
Depression: NCT05680220

Auditory gamma stimulation is being tested for traumatic (blast-related) brain injury (NCT03836976)

Vibration gamma stimulation is being tested for insomnia (NCT06983275)

Audio-visual gamma stimulation approaches are being tested in trials for:
Alzheimer's disease: NCT06595511 (with cognitive training); NCT05206305; NCT05637801

Individuals at risk for AD: NCT05776641
Multiple sclerosis: NCT07310862 (for fatigue)
Schizophrenia: NCT07342465
Parkinson's disease: NCT06295458 (motor symptoms); NCT05268887 (motor and cognitive symptoms)
Cognitive aging: NCT06229093
Down Syndrome: NCT05196984

Electrical:

Transcranial Alternating Current (tACS) approaches are being tested in trials for:
Healthy older adults: NCT06740864; NCT06284720; NCT04732533
Alzheimer's disease/MCI: NCT07230158; NCT06202872; NCT05708001; NCT06547021
Neurodegenerative diseases: NCT05326750
Frontotemporal degeneration: NCT04425148
Delirium: NCT06522087; NCT06460363
COPD: NCT07332169

Magnetotherapy gamma stimulation is being tested for stroke (NCT06551597)

Photobiomodulation gamma approaches are being tested for cognitive outcomes in trials for:
MCI: NCT06618807
Survivors of childhood cancer: NCT05550948
Healthy adults: NCT07209683

Search terms:
Pubmed, Google: 40 Hz, gamma stimulation

- Alzheimer's disease, neurodegeneration, cognition, clinical trial, safety

Websites visited for Gamma Stimulation:

- Clinicaltrials.gov

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