

Literature Review

InT BioHackathon | Team 24 | Mateo Umaguing, John Walkiewicz, Logan Umaguing

Include proper citation (APA please!) and important takeaways. To prevent people from reviewing the same articles, **check this sheet to make sure that the lit isn't reviewed yet**. Remember that once you open an article, you should immediately add the citation so that we know what's available to review and what isn't. The example citation and review for an article is in blue.

Red means the citation is improperly formatted (I'm using a Google Docs extension to automatically format sources); I'll fix them later. - Mateo

Citations and Review

(Author(s), Year)

- “Title” *remember the quotes*
 - important detail 1 *ostensibly the abstract*
 - important detail 2 *info relevant to us*
 - important detail 3 *info relevant to us*
 - important detail 4 *info relevant to us*
 - important detail 5 *info relevant to us*
-

(Manippa et al., 2022)

- “An update on the use of gamma (multi)sensory stimulation for Alzheimer’s disease treatment”
- Gamma Entrainment Using Sensory stimulation (GENUS) is a promising approach to treating AD.
- “From a neuropathological perspective, AD is characterized by the accumulation of extracellular β -amyloid ($A\beta$) plaques and intracellular neurofibrillary tangles of phosphorylated tau protein (p-tau) in the brain, which initiates a neurotoxic cascade of progressive neuronal and synaptic loss in the hippocampus and surrounding medial temporal lobe (Bloom, 2014), and general brain atrophy (Pini et al., 2016). These alterations lead to imbalanced neuronal activity, reduced neuronal synchrony, and disrupted oscillatory activity at local and network levels (Mucke and Selkoe, 2012; Das et al., 2018). The available pharmacological treatments for AD show limited efficacy (Kumar and Singh, 2015); therefore, recent studies point toward alternative therapeutic avenues, such as non-invasive brain stimulation (NIBS), and multisensory stimulation targeting the restoration of abnormal brain oscillations (Menardi et al., 2021; Traikapi and Konstantinou, 2021).” - These are recent articles from 2021. Make sure that they are peer-reviewed and replicable. This can be part of the research proposal, i.e. “validation of NIBS and multisensory stimulation therapeutic benefits in [rodents or humans?] with AD symptoms.”
- “Indeed, gamma oscillations (γ , > 30 Hz) exert a key role in a multitude of sensory and high-order cognitive functions (Fries, 2005; Cole and Voytek, 2017; Grent-T-Jong et al.,

2018), such as episodic memory and executive functions (Carr et al., 2012; Buzsáki, 2015; Gonzalez-Perez et al., 2019), by orchestrating intra-brain communication (Ribary et al., 1991; Jefferys et al., 1996). Consistent evidence from both murine models of the disease (Yamamoto et al., 2014; Iaccarino et al., 2016) and clinical studies (Mably and Colgin, 2018) link memory and cognitive impairments to aberrant or reduced brain activity in the gamma band." - Which regions of the brain are being deactivated? We should review the cited literature in order to figure out if we know what activity in which regions we can target. We will need to use rodent models, histology, and more.

- Iaccarino et al. 2016 used 5XFAD mouse model of AD
- "Specifically, gamma-band activity is thought to arise from the activity of fast-spiking populations of GABAergic interneurons, namely parvalbumin-positive (PV+) cells (Rivolta et al., 2015). Restoration of PV+ interneurons in the hAPP mice has been found to exert a beneficial effect on gamma rhythmicity and memory (Verret et al., 2012). Noteworthy, aberrant gamma activity, particularly at 40 Hz, has been reported even before plaque formation in both rodents and humans, suggesting that E/I imbalance and gamma alterations preceded molecular alterations in the AD neuropathological cascade (Iaccarino et al., 2016; Etter et al., 2019). This evidence has implications for the potentiality of gamma abnormality as an early biomarker of AD, as well as a therapeutic target (Goutagny et al., 2013; Mably and Colgin, 2018)." - "implications for the potentiality" is vague. I'm sure the paper covers this, but if not, we should do a thorough LFP study(?) EEG study of AD patients' and their genetically predispositioned relatives' gamma bands. We can then ascertain if there is a statistically significant difference between the gamma band power of AD patients', GPADRs', non-AD patients, and regular populations' EEG signals-LFP signals. TO-DO: add stat test.
- Can calcium imaging (Miniscope, fiber photometry) data be correlated with LFP band power? We can induce these oscillations in rodents, record their neural activity with both fibro, miniscope data, and LFP. This will give us a spatiotemporally precise and accurate measure of which regions are differentially active/inactive during induced periods of induced gamma oscillation or AD symptoms. The induced gamma oscillation can come from optogenetics.
- Question: what EEG signal band do dopaminergic projections occupy? I have general interests in the relation between dopamine levels, neuromodulation of such signals via optogenetics, chemogenetics, psychiatric medications, and other substances (alcohol, cannabis, etc.).
- We need to consult AD researchers at UCLA about this type of neuromodulation and what has/vs what hasn't been done. I am going to also consult some EEG centered researchers and see what the best way to go about this is. We DON'T need to pursue this idea I have, but I am going to save this idea for the future.
- Optogenetics in mice, LFP recordings in rodents, and GENUS. GENUS is sensory/auditory stimulation to induce gamma oscillations. I need to find out how effective this is.

- “Intermittent Light Exposures in Humans: A Case for Dual Entrainment in the Treatment of Alzheimer’s Disease”
-

(Byron et al., 2021)

- “Mutual Interactions between Brain States and Alzheimer’s Disease Pathology: A Focus on Gamma and Slow Oscillations”
-

(“Optogenetic Neuromodulation with Gamma Oscillation as a New Strategy for Alzheimer Disease: A Narrative Review,” 2022)

- “Optogenetic Neuromodulation with Gamma Oscillation as a New Strategy for Alzheimer Disease: A Narrative Review,”
- THIS PAPER IS LIT ;)
- Ko & Yoon, 2022
- <https://doi.org/10.12701%2Fjyms.2021.01683>
- “Since the loss of $\alpha 4\beta 2$ nicotinic receptors is increased in AD [64-67], acetylcholine is released synaptically by optogenetic stimulation [68]. Bell et al. [68] suggested that activation of $\alpha 4\beta 2$ receptors mediates nicotinic excitatory postsynaptic potential (EPSP) in CA1 interneurons by affecting the stratum lacunosum-moleculare using retroviral AAV expressing oChIEF in a Cre-dependent manner. Optogenetic activation of pyramidal neurons in the entorhinal cortex layer III improves synaptic defects between pyramidal neurons and CA1 parvalbumin-positive neurons in transgenic AD mice. It also halts the decrease in spatial learning and memory [69]. Although AAV has been generally used as a viral vector, the incidence of sharp wave ripples is reduced by optogenetic stimulation at the target location. The medial septum cholinergic stimulation of sleeping animals decreases sharp-wave ripples and advances theta-gamma oscillations. This research highlights the significance of the timing of cholinergic input. This could explain the limited success of cholinesterase inhibitor drugs in AD [70].

Optogenetic inhibition of hilar GABAergic interneurons of the dentate gyrus (DG) through Cre-dependent gene expression of enhanced halorhodopsin disrupts spatial learning and memory retrieval without affecting short-term working memory, motor coordination, and memory retention. Using optogenetic stimulation, GABAergic interneurons can be activated without affecting pyramidal neurons in the CA3 and CA1 regions [71]. Optogenetic stimulation of hippocampal memory engram cells in transgenic AD mice overexpressing APP/presenilin-1 induces memory retrieval. Optogenetic stimulation of DG engram cells improved long-term memory and spine density [72]. Optogenetic stimulation of the DG in APP/presenilin-1 \times ArcCreERT2 \times channelrhodopsin-2-enhanced yellow fluorescent protein mice improved memory impairment. Stimulation of DG neural ensembles leads to enhancement of memory retrieval and reactivation of neural ensembles [73], which suggests that optogenetic DG manipulation could be a target for AD treatment.”

Optogenetic activation of glutamatergic neurons in A β -injected mice improves working memory and short-term memory without affecting long-term memory in the bilateral DG. This stimulation downregulates A β and upregulates neuronal nuclei, which are biomarkers of neuroprotection [10]. As antagonism of adenosine A2A receptor (A2AR) mimics memory impairment prevention in AD animal models [74-77], optogenetic activation of a chimeric rhodopsin-adenosine A2AR protein activates cyclic adenosine monophosphate (cAMP) signaling, which increases cAMP levels and mitogen-activated protein kinase phosphorylation. This activation induces memory dysfunction in the hippocampus through phospho-CREB signaling [77]. These reports suggest that multiple, targeted optogenetic approaches can be used to treat AD [10].” Should we just optogenetically stimulate the entire hippocampus?

- “Since the excitation of gamma oscillations reduces circuit noise and amplifies signals that result in an increase in the signal transmission of the neocortex [49], optogenetics-induced gamma oscillations may have therapeutic potential for AD. Studies on the applications of optogenetics to 40-Hz gamma oscillations have been ongoing since the optogenetic stimulation of fast-spiking parvalbumin-positive interneurons in gamma oscillations was first demonstrated in mice [78]. Entrainment or synchronization of hippocampal gamma oscillations and spiking to 40 Hz via noninvasive stimuli, such as flashing lights or pulses of sound [79], reduces the A β load and activates microglia in a well-established 5XFAD mouse model of AD [80].

Decreased amyloidogenesis and increased amyloid endocytosis can be mediated by microglia [80]. Co-localization of microglia and A β was confirmed by histological analysis and induction of genes related to morphologic transformation of microglia was confirmed by gene expression profiling. That study suggested a neuroprotective role of gamma oscillations that affect neurons and microglia. Gamma oscillations also decrease phosphorylated tau protein levels [80].

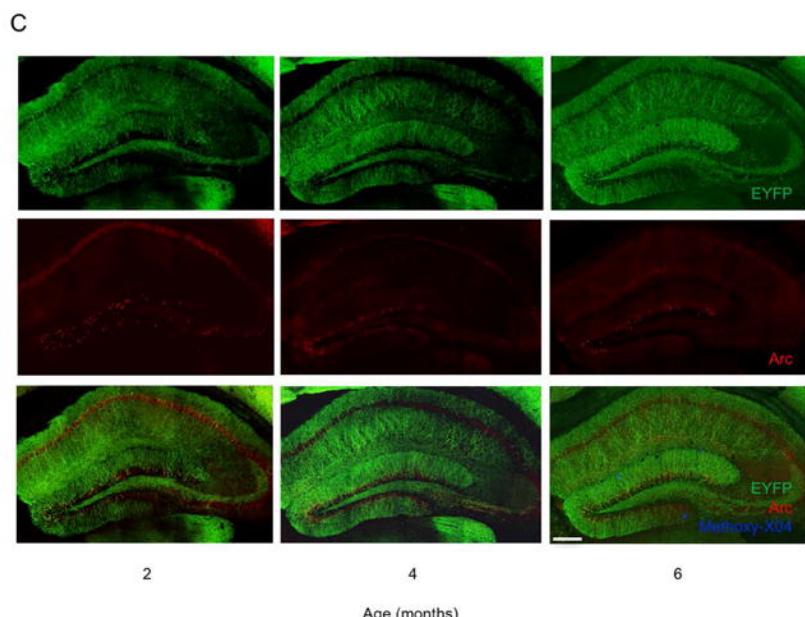
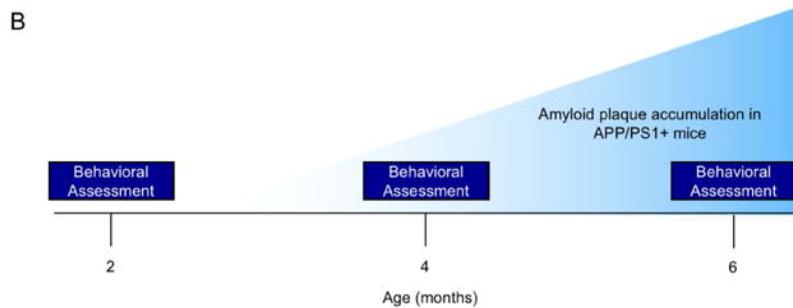
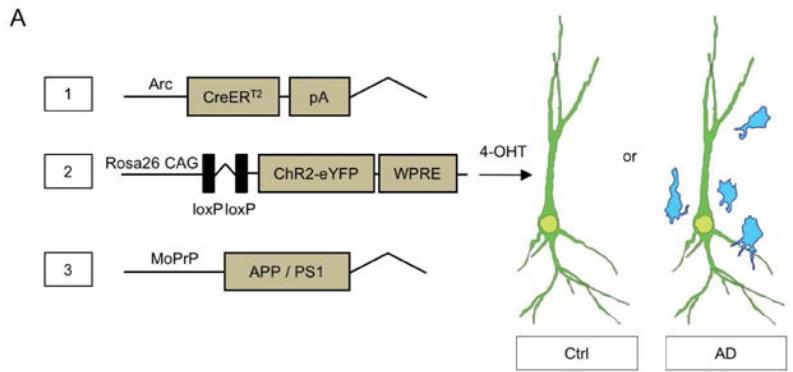
In the JA20 AD mouse model, optogenetic stimulation of parvalbumin-positive interneurons restores slow gamma oscillations and increases spatial memory [47]. Accumulation of A β 1-42 oligomers disrupts long-term potential and theta-nested gamma oscillations in the hippocampus. Furthermore, stimulation of GABAergic interneurons reduces neuroinflammation and activates autophagy. Photostimulated APP/presenilin-1 mice showed a significant decrease in escape latency in the Morris water maze test, indicating that optogenetic stimulation ameliorates spatial learning [81]. Optogenetic modulation of channelrhodopsin-2-expressing parvalbumin-positive interneurons restores gamma oscillations and gamma oscillation-induced spike timing-dependent long-term potentiation [82]. This activation selectively increases spontaneous inhibitory postsynaptic currents at theta and gamma frequencies and restores A β -induced reductions [83].

However, activation of parvalbumin-positive neurons by 40-Hz optical stimulation in the basal forebrain increased A β 1-42 levels. Accumulation of amyloid plaques was increased in the medial prefrontal cortex and the septal nuclei. These results indicate

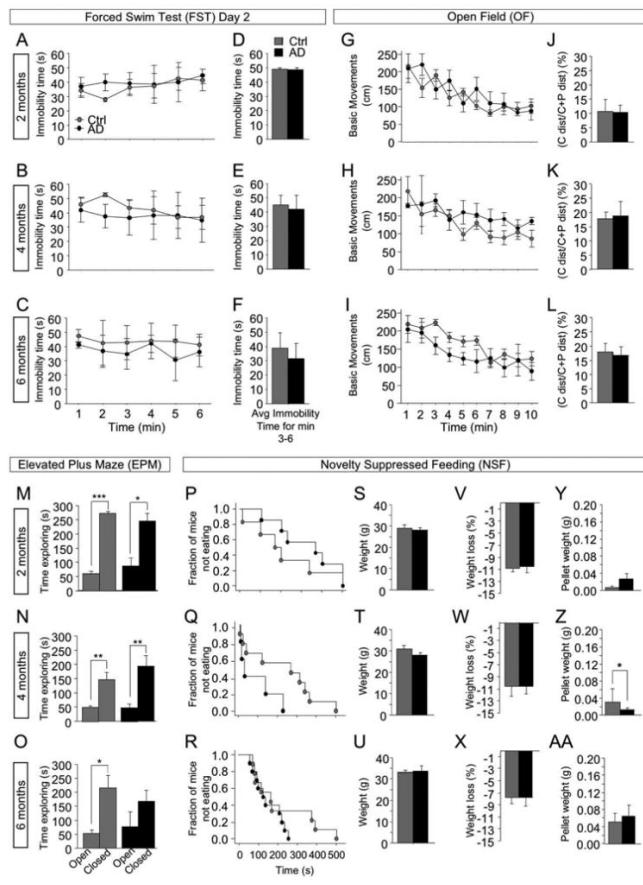
that the method of activation of gamma oscillations changes the modulation of A β plaques [84]. Optogenetic stimulation of double-frequency slow waves increased the disruption of calcium homeostasis by A β and induced synaptic spine loss [85]. Subsequent human clinical trials of gamma oscillation band stimulation have shown mild cognitive improvements in patients with AD who have been exposed to light, sound, or tactile stimuli in the 40-Hz range [44]. However, the precise molecular and cellular mechanisms by which gamma oscillation band stimulation ameliorates AD pathology are unknown.

- “Further research is needed to determine how optogenetics might be associated with gamma oscillations, and we suggest that, based on studies to date, it is highly related to the continuity of excitation-inhibition signals, frequency of gamma oscillations, and cytokine production-related cell signaling.”
- lol deep learning insert “As deep learning technology advances, the artificial manufacturing of opsins or modulation of viral vectors could be a breakthrough in optogenetic technology.”
- s: entorhinal cortex layer III pyramidal neurons -> improves synaptic defects and spatial learning & memory losses [69]
 - <https://doi.org/10.1038%2Fmp.2016.151>
 -
 - ECII regions
 - 473 nm laser
 - 10 s intervals, 10 trains
 - ITI?
 - train - 4 100Hz spikes repeated 10 times at 5 Hz; each spike is 5 ms
 - PD range: [0.1, 5] mW mm⁻²
 - once per day for 35 consecutive days
 - experiments done 25 days post treatment
- s: medial septum cholinergic in sleeping animals -> decreases sharp-wave ripples, advances theta-gamma oscillations [70]
 - <https://doi.org/10.7554%2Feliife.65998>
 -
 - habituate mice 2 days -> stopped moving -> 30 s long stim
 - 473 nm
 - 25 pm 1 mW
 - 50 ms long pulses, 10 Hz
 - 60-120 s interval w/o stimulation
 - Y-maze task: laser activated in goal zone on alternating trials for within-subject comparison
- s: GABAergic interneurons w/o affecting CA3 and CA1 regions [71]
 - inhibition of GABAergic interneurons impaired spatial learning
 - <https://doi.org/10.1371%2Fjournal.pone.0040555>

- 594 nm
 - 1 mW intensity
 - Morris Water Maze
 - stimulate hilus of hippocampi
 - 60 s illumination during various tasks
-
- s: hippocampal memory engram cells -> memory retrieval, improved long-term memory and spine density [72]
 - <https://doi.org/10.1038%2Fnature17172>
 - AD model: delta exon 9 variant of presenilin-1 w/ amyloid precursor protein
 - 460 nm
 - delay onset of 25 us
 - power: 33 mW/mm²
 - single light pulse of 1 s repeated 10 times every 5 s
-
- s: dentate gyrus -> improved memory impairment, memory retrieval and reactivation of neural ensembles [73]
 - <https://doi.org/10.1002%2Fhipo.22756>
 - APP/PS1 model

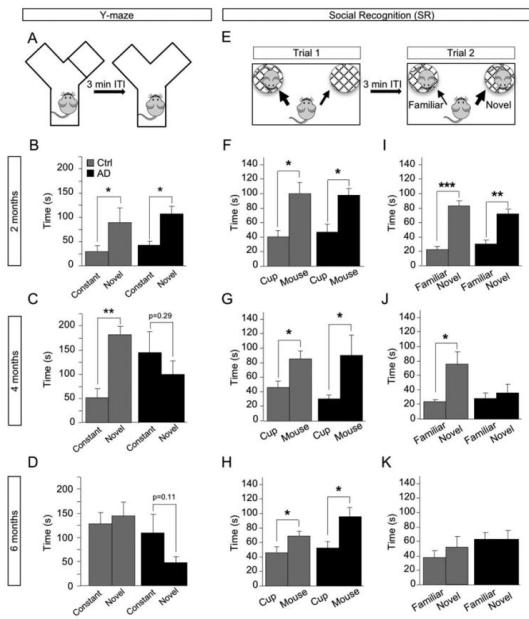


- depressive- and anxiety-like behavior not altered in AD
 - immobility
 - movements
 - distance traveled in center



○
○ **▲▲**

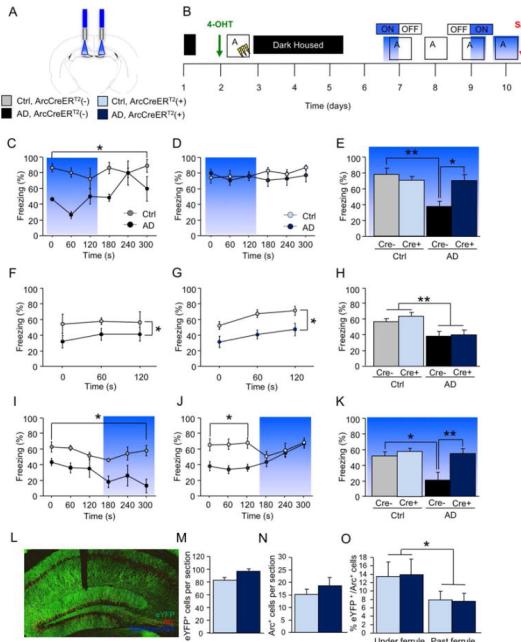
- spatial working memory and social recognition is impaired by AD
 - unbaited Y-maze



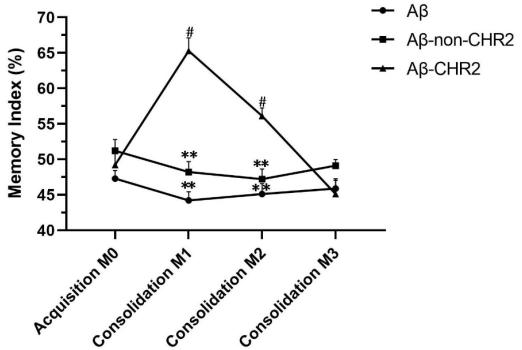
○

- contextual fear memory is impaired by AD

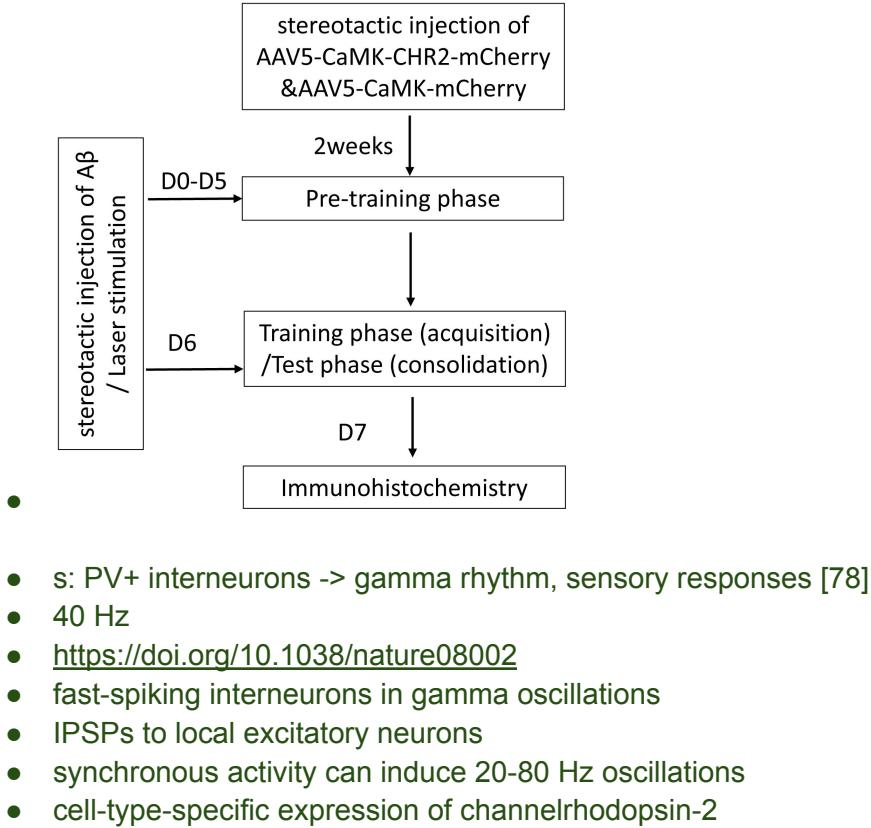
- 1-shock or 3-shock CFC procedures
- opto stimulation of CFC DG trace improves memory retrieval



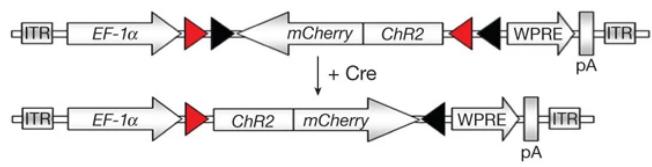
- fiber optics implanted directly above DG
- opto for 3 minutes
 - 2-3 mW, 10 Hz stimulation at 20 ms pulses
- s: glutamatergic neurons in bilateral dentate gyrus -> improves working memory and short-term memory [10]
- <https://doi.org/10.3389%2Ffnins.2020.583628>
- amyloid beta injected mouse model
- behavioral test:
 - explore arena for 5 min a day 1-5 days after AB injection
 - day 6: look at 2 objects for 3 min
 - 5 min, 2 hr, 24 hr after day 6: measure memory with new object



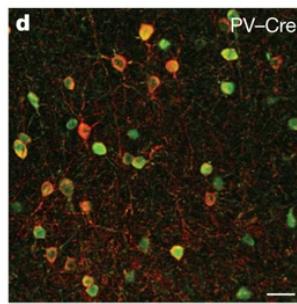
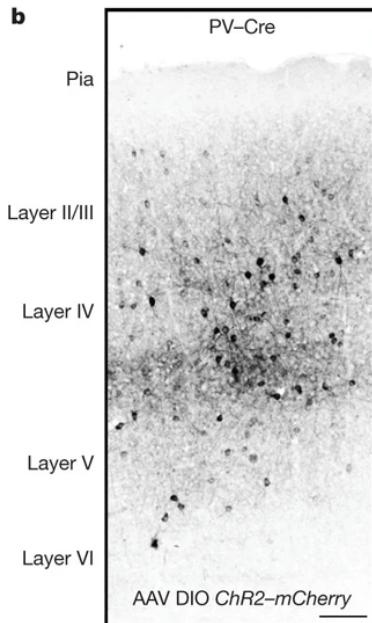
- 473 nm, 1-3 ms, 10 Hz, 5 min
- once a day for 7 days



a AAV DIO *ChR2-mCherry*

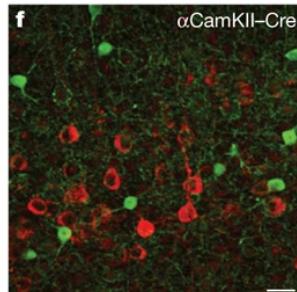
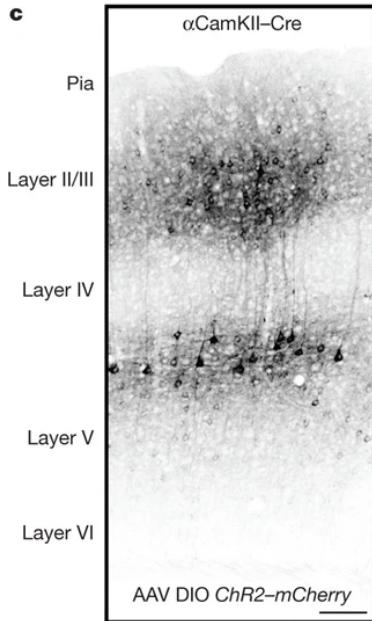


b

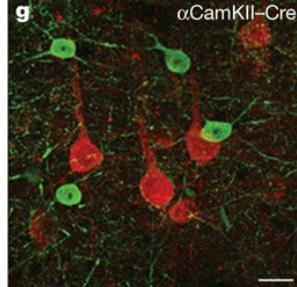


PV ChR2-mCherry

c



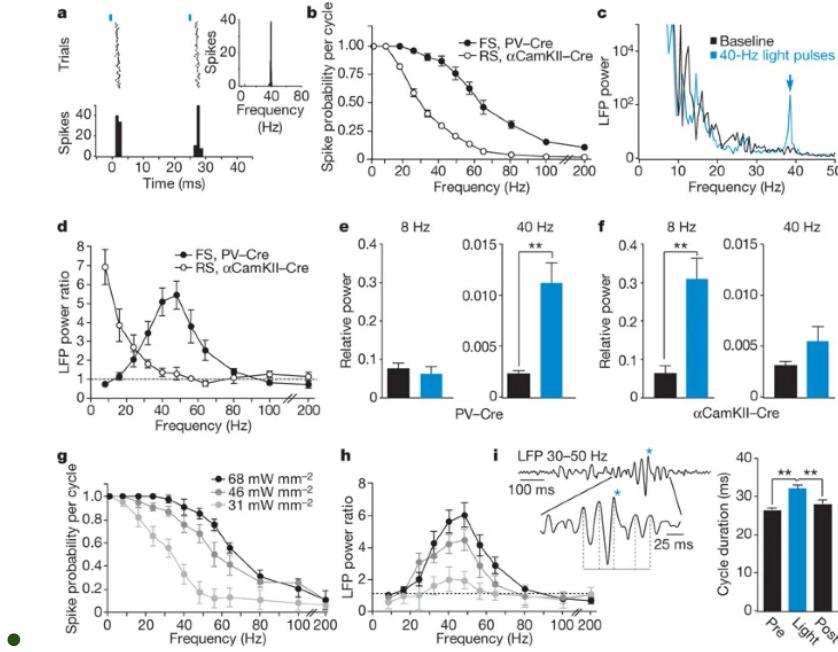
PV ChR2-mCherry



α CamKII-Cre

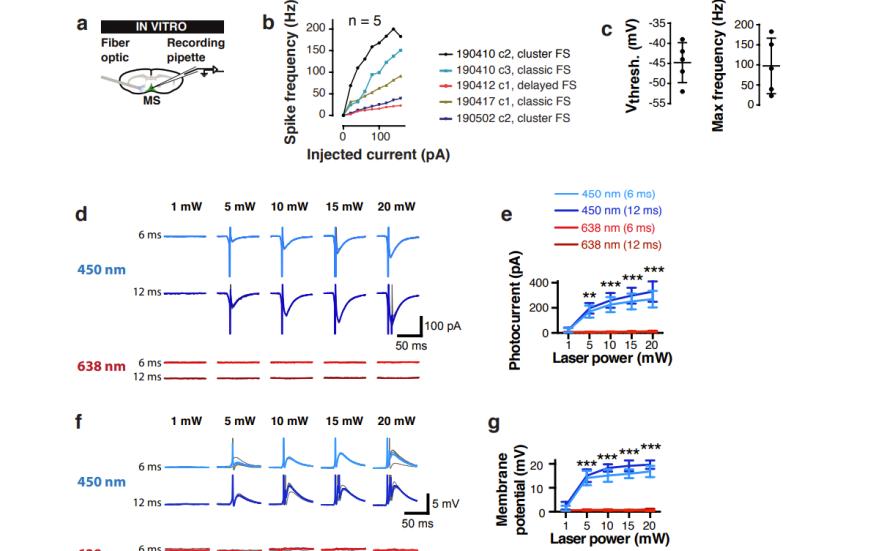
-

- 1-ms light pulses
- 40 Hz at 25-ms intervals

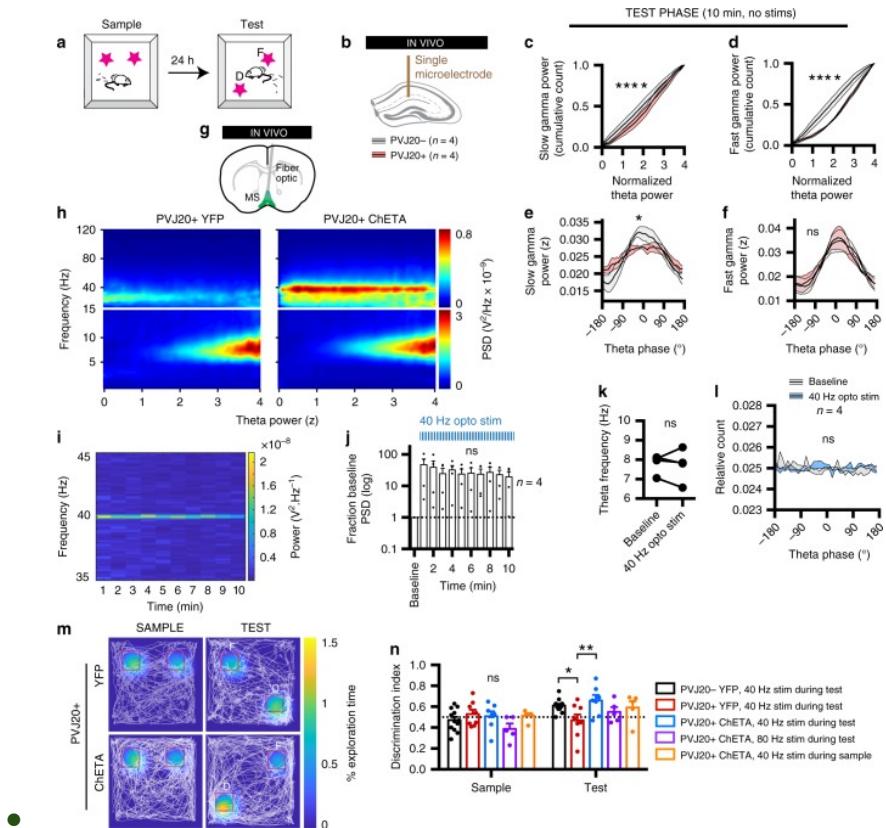


- s: hippocampal gamma oscillations -> reduces AB load and activates microglia [80]
- <https://doi.org/10.1038%2Fnature20587>
-
- 40 Hz, 5XFAD
- 5XFAD have reduced gamma power
- 1-ms 473 nm 40 Hz, verified with LFP
- FS-PV interneurons
- reduced AB stuff after 1 hr of stimulation
- CA1

- s: PV+ interneurons -> slow gamma oscillations, spatial memory [47]
- <https://doi.org/10.1038%2Fs41467-019-13260-9>
-
- J20-APP AD model
- medial septum PV cells
- ChETA
- 40 Hz, 12 ms pulses
- 10-20 mW power



- “saves gamma rhythms”



- familiar object placement paradigm

- 5s ON, 5s OFF during task

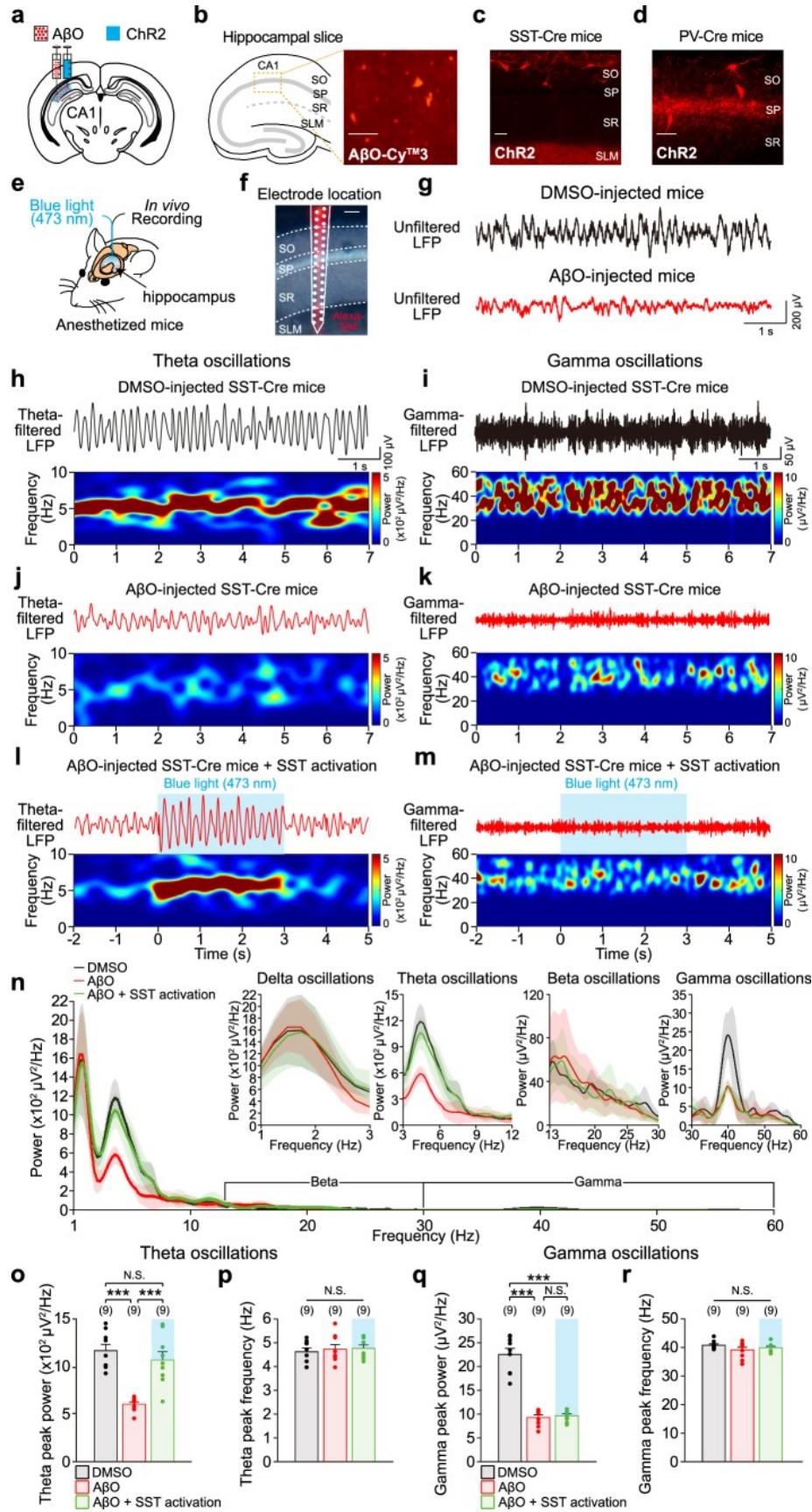
- s: GABAergic interneurons → reduced neuroinflammation, decrease in escape latency (ameliorated spatial learning) [81]

- <https://doi.org/10.1016/j.bbrc.2020.03.004>

- 473 nm laser
- CA1 neurons
- 2 mW/mm²
- 50 Hz, 10ms on, 10 ms off sustaining 30 min
- Morris Water Maze
- GABAergic neurons in the CA1
- 16 channel microelectrode array to measure LFP

- s: PV+ interneurons -> restore gamma oscillations, LTP [82]
- <https://doi.org/10.1186%2Fs12915-019-0732-7>
- CA1
- 5 Hz sinusoidal 470 nm light
- Arduino-based controller
- 0 to 15 mW
- use Welch's PSD on LFP recordings to find frequency that maximizes gamma oscillations

- s: ^^^ -> increases ISPS @ theta & gamma freqs and restores AB-induced reductions [83]
- ABO injected mouse model of AD
 - reduced peak theta and gamma power
- 473 nm
- SST interneurons -> theta power goes up, but not gamma
- PV interneurons -> gamma power goes up
- "Optogenetic activation of PV interneurons selectively restores the hippocampal gamma oscillations impaired in AβO-injected mice"
- <https://doi.org/10.1007%2Fs00429-020-02044-3>
- 50% max intensity
- 3s, 60s ITI, 10 repetitions
- Neuronexus 32 channel probe for LFP recording



- s: PV+ optical stimulation in basal forebrain -> increased AB1-42 levels [84]
- <https://doi.org/10.1038%2Fs41598-020-72421-9>
-
- 40 Hz
- what is optical stimulation
 - optogenetics (why didnt they just say that)
- “The induction of cortical gamma oscillations by optogenetic stimulation of basal forebrain PV+ neurons”
- 5xFAD
- Cortical EEGs
- basal forebrain
- 470 nm
- 114–178 mW/mm²
- 10 min baseline recording -> 1 hr stim

(McDermott et al., 2018)

- “Gamma Band Neural Stimulation in Humans and the Promise of a New Modality to Prevent and Treat Alzheimer’s Disease”

(“Multi-Sensory Gamma Stimulation Ameliorates Alzheimer’s-Associated Pathology and Improves Cognition,” 2019)

- “Multi-Sensory Gamma Stimulation Ameliorates Alzheimer’s-Associated Pathology and Improves Cognition,”
-

(Götz et al., 2018)

- “Rodent models for Alzheimer disease”

(Iaccarino et al., 2016)

- “Changes in gamma oscillations (20-50 Hz) have been observed in several neurological disorders. However, the relationship between gamma and cellular pathologies is unclear. Here, we show reduced behaviorally-driven gamma before the onset of plaque formation or cognitive decline in a mouse model of Alzheimer’s disease (AD). Optogenetically driving FS-PV-interneurons at gamma (40 Hz), but not other frequencies, reduced levels of amyloid-β (A β)1-40 and A β1-42 isoforms. Gene expression profiling revealed induction of genes associated with morphological transformation of microglia and histological analysis confirmed increased microglia co-localization with A β.
- Subsequently, we designed a non-invasive 40 Hz light-flickering paradigm that reduced A β1-40 and A β1-42 levels in visual cortex of pre-depositing mice and mitigated plaque load in aged, depositing mice. Our findings uncover a previously unappreciated function of gamma rhythms in recruiting both neuronal and glial responses to attenuate AD-associated pathology.”

(Li et al., 2023; Yin et al., 2019)

("Gamma Entrainment Binds Higher-Order Brain Regions and Offers Neuroprotection," 2019)

(Bystritsky et al., 2011)

Table 1 Comparison of LIFUP with other common neuromodulation treatment modalities

Biophysics	Stimulation modality	Deep brain stimulation (DBS)	Transcranial magnetic stimulation (TMS)	Focused ultrasonic pulsation (LIFUP)
Energy delivery	Electrical	Magnetic	Mechanical (most likely)	
Invasiveness	Invasive	Noninvasive	Noninvasive	
Stimulation source	Voltage/current source + electrical conducting probe	Alternating magnetic field	Low intensity pulsating ultrasound	
Stimulation configuration	Implantable electrodes	Magnetic coils	US transducer	
Biophysical principle	Direct conduction	Faraday induction	Ion channel alternation	
Spatial resolution	Fractions of mm	~3-5 cm	2-5 mm	
Depth of penetration	Unlimited	~1-1.5 cm unless H coil is used	10-15 cm or more	
Duration of the neuromodulation effect after the stimulation is stopped	~5 s	~5 s	Possibly ~10-40 mins	
Use with fMRI for brain mapping (simultaneously)	Possible but difficult	Possible but difficult	Could be used simultaneously	
Use with fMRI to guide the treatment and evaluate the effect	Used for implantation	Has been used	Could be used	

(Design, Development, and Operation of a Low-Intensity Focused Ultrasound Pulsation (LIFUP) System for Clinical Use, n.d.)

(Arulpragasam et al., 2022)

<https://doi.org/10.1016/j.neuron.2010.05.008>

LIFUP rat

<https://doi.org/10.1016/j.ultrasmedbio.2014.01.020>

LIFUP mouse

<https://doi.org/10.1038/nprot.2011.371>

LIFUP

(Bystritsky et al., 2011)

("Sleep and Alzheimer's Disease," 2015)

- "Sleep disorders are frequent in Alzheimer's disease (AD), with a significant impact on patients and caregivers and a major risk factor for early institutionalization. Micro-architectural sleep alterations, nocturnal sleep fragmentation, decrease in nocturnal sleep duration, diurnal napping and even inversion of the sleep-wake cycle are the main disorders observed in patients with AD. Experimental and epidemiological evidence for a close reciprocal interaction between cognitive decline and sleep alterations is growing. Management of sleep disorders in AD is pre-eminently behavioral. Association of melatonin and bright light treatment seems to be promising as well. The

presence of sleep complaints, especially excessive somnolence in demented patients, should draw attention to possible associated sleep pathologies such as sleep apnea syndrome or restless legs syndrome.”

<https://doi.org/10.1038/nprot.2007.44>

- elevated plus maze

<https://doi.org/10.1016/j.neurobiolaging.2015.07.001>

- “Progressive age-related changes in sleep and EEG profiles in the PLB1Triple mouse model of Alzheimer’s disease”
- EEG changes during sleep

(“Low-Intensity Focused Ultrasound Pulsation Device Used During Magnetic Resonance Imaging: Evaluation of Magnetic Resonance Imaging-Related Heating at 3 Tesla/128 MHz,” 2014)

- EEG effects have not been studied in this article
- “MRI performed at relatively high specific absorption rate (SAR) caused a slight elevation in temperature ($\leq 0.6^{\circ}\text{C}$). Concurrent use of MRI at a medium-strength SAR and LIFUP sonication resulted in maximum temperature rise of 3.1°C after 8 min of continuous use.”
- “Under the specific conditions utilized for this investigation, LIFUP sonication does not appear to present significant heating risks when used concurrently with MRI. This information has important implications for the use of the LIFUP sonication in human subjects undergoing MRI at 3 T/128 MHz.”

<https://doi.org/10.1038/s41596-018-0021-x>

- how to look at AB levels

(Hart et al., 2003)

- **Aim:** To document the behavioral and psychological symptoms in patients with a diagnosis of established Alzheimer’s disease (AD) for at least 3 years.
- **Methods:** Patients with a 3 year history of AD (NINCDS/ADRDA) were recruited from old age psychiatrists and elderly care memory clinics. Information regarding duration of symptoms and non-cognitive symptomatology was obtained during an interview with a carer or next-of-kin who had contact with the patient at least 3 times a week and for at least 3 years. MMSE,FAST and NPI including caregiver distress, were used to assess cognition, function and behavioral/psychological disturbance respectively. With each non-cognitive symptom the carer was asked to estimate its onset.
- **Results:** The mean age of patients was 77 years and duration of illness 87 months. Mean MMSE was 8/30 and FAST score (6d). Of the psychological symptoms occurring at any stage, depression (56%), delusions (55%) and anxiety (52%) were most common, with hallucinations, elation and disinhibition occurring less frequently. In general, behavioral changes were more common with apathy occurring in 88% of patients, motor behavior in 70%, aggression in 66%, irritability and appetite changes in 60% and sleep

disturbance in 54%. All symptoms except apathy became less common when the carer was asked if they were still present in the last month. Mean onset of psychological symptoms was 47 months. Mean onset of behavioral symptoms was 48 months. Behavioral disturbance seemed to cause more care-giver distress than psychological change.

- **Conclusion:** The results show behavioral and psychological symptoms in AD are common and distressing for carers. They appear to require a consistent period of neurodegeneration in order to emerge.”

(Dewachter et al.. 2000)

- Transgenic mice that overexpress wild-type or mutant APP recapitulate part of AD pathology, evidenced by the presence of amyloid plaques, cognitive deficits, behavioral deficits and other traits.
- No model contains all aspects of AD pathology or all pathological lesions in the brain, with especially the formation of neurofibrillary tangles and its contribution to the pathology, if any, still lacking.

(Johnson-Wood et al..1997)

- While absolute levels of APP expression likely contribute to the rate of amyloid β-peptide (Aβ) deposition, regionally specific factors also seem important, as homozygotic mice express APP levels in pathologically unaffected regions in excess of that measured in certain amyloid plaque-prone regions of heterozygotic mice
- Regional levels of APP and APP-β were nearly constant at all ages, while Aβ levels dramatically and predictably increased in brain regions undergoing histochemically confirmed amyloidosis, most notably in the cortex and hippocampus. In hippocampus, Aβ concentrations increase 17-fold between the ages of 4 and 8 months, and by 18 months of age are over 500-fold that at 4 months, reaching an average level in excess of 20 nmol of Aβ per g of tissue.

(Sturchler-Pierrat et al. 1997)

- Numerous attempts focusing on transgenic expression of human APP (14–19) have been made to obtain a valid animal model of AD. However, only two transgenic mouse lines have been described that develop Aβ deposits characteristic of AD.
- Two of these lines that differ in transgene-derived APP expression levels and FAD mutations develop plaque-like Aβ deposits in neocortex and hippocampus to different degrees. They also display additional aspects of AD pathology not commonly associated with the Aβ peptide.

(Lecanu et al 2013)

- Transgenic models still represent the golden standard. However, if we consider contributions to drug development and release to the market the ultimate validation of an animal model, we must admit that there is room for different types of animal models. It is especially crucial to stress that rat and mouse transgenic models of AD

address only the familial form of the disease, which barely represents 5% of AD cases.

[\(Carradori et al. 2018\)](#)

- Treatment of AD-like transgenic mice with anti-A β_{1-42} -functionalized nanoparticles led to: (i) complete correction of the memory defect; (ii) significant reduction of the A β soluble peptide and its oligomer level in the brain and (iii) significant increase of the A β levels in plasma.
- NOR is a memory test which relies on spontaneous animal behavior without the need of stressful elements such as food or water deprivation or electric foot shock.⁴⁷ In the NOR mice are introduced into an arena containing two identical objects that they can explore freely. Twenty-four hours later mice are reintroduced into the arena, containing two different objects one of which previously presented (familiar) and a new completely different one (novel). Animals with no memory impairment spent longer time investigating the novel object, giving a higher discrimination index.

[\(Tsai et al, 2007\)](#)

- Most of the current clinical treatments for Alzheimer's disease (AD) are largely symptomatic and can have serious side effects. We have tested the feasibility of using the granulocyte colony-stimulating factor (G-CSF), which is known to mobilize hematopoietic stem cells (HSCs) from the bone marrow into the peripheral blood, as a therapeutic agent for AD. Subcutaneous administration of G-CSF into two different β -amyloid (A β)-induced AD mouse models substantially rescued their cognitive/memory functions.
- Mice were first trained in the Morris water maze task.
- Chat GPT's description of Morris water maze task:
- The water maze consists of a large circular pool filled with water, opaque and usually made dark to prevent the animals from seeing through it. The pool contains a hidden platform submerged just below the water's surface. The goal of the task is for the animal to locate and climb onto the platform, which provides a stable escape from the water.
- The task is conducted over several trials, typically spanning multiple days. During each trial, the animal is released into the pool from different starting points and must swim to find the hidden platform. Various visual cues, such as colored shapes or patterns on the walls, are placed around the room to provide spatial reference points.
- The main measure of performance in the Morris water maze is the time it takes for the animal to locate the platform. Initially, animals tend to swim randomly, but over repeated trials, they gradually learn the spatial location of the platform. This learning is reflected in a decrease in the time taken to find the platform and in the

adoption of more efficient search strategies, such as swimming directly towards the platform.

- The water maze task is often used to assess spatial learning and memory abilities and investigate the effects of various factors on cognitive performance. It has been extensively used to study the role of the hippocampus, a brain region crucial for spatial navigation and memory formation. Researchers can also introduce experimental manipulations, such as pharmacological treatments or genetic modifications, to examine their effects on learning and memory in the water maze.

<https://doi.org/10.1093/cercor/bhz122>

<https://doi.org/10.1038%2Fs41386-020-0778-9>

- PV+ interneurons communicate with pyramidal neurons

<https://doi.org/10.1523%2FJNEUROSCI.0990-16.2016>

- gamma?

<https://doi.org/10.3389/fncir.2019.00073>

- bred Vgat-Cre mice
- injection into VTA

<https://doi.org/10.3389/fncel.2021.688905>

- more chemo

<https://doi.org/10.1007/s00702-017-1697-8>

- opto and chemo in primates

<https://doi.org/10.1016/j.coph.2022.102204>

- chemo in primates

<https://doi.org/10.1111/ner.12075>

korb LIFUP

<https://doi.org/10.1016/j.cub.2013.10.029>

more LIFUP

<https://doi.org/10.1093/cz/zow070>

oculus rodent

GENERATING DATA

<https://doi.org/10.1152/jn.2000.84.1.390>

<https://doi.org/10.1152/jn.2000.84.1.401>

Abbreviations

- AD = Alzheimer's Disease
 - NIBS = non-invasive brain stimulation
-

Full citations

- Arulpragasam, A. R., van 't Wout-Frank, M., Barredo, J., Faucher, C. R., Greenberg, B. D., & Philip, N. S. (2022). Low Intensity Focused Ultrasound for Non-invasive and Reversible Deep Brain Neuromodulation—A Paradigm Shift in Psychiatric Research. *Frontiers in Psychiatry / Frontiers Research Foundation*, 13. <https://doi.org/10.3389/fpsyg.2022.825802>
- Byron, N., Semenova, A., & Sakata, S. (2021). Mutual Interactions between Brain States and Alzheimer's Disease Pathology: A Focus on Gamma and Slow Oscillations. *Biology*, 10(8), 707.
- Bystritsky, A., Korb, A. S., Douglas, P. K., Cohen, M. S., Melega, W. P., Mulgaonkar, A. P., DeSalles, A., Min, B. K., & Yoo, S. S. (2011). A review of low-intensity focused ultrasound pulsation. *Brain Stimulation*, 4(3). <https://doi.org/10.1016/j.brs.2011.03.007>
- Design, Development, and Operation of a Low-Intensity Focused Ultrasound Pulsation (LIFUP) System for Clinical Use.* (n.d.). Retrieved May 26, 2023, from <https://ieeexplore.ieee.org/document/9131840>
- Figueiro, M. G., & Leggett, S. (2021). Intermittent Light Exposures in Humans: A Case for Dual Entrainment in the Treatment of Alzheimer's Disease. *Frontiers in Neurology*, 12. <https://doi.org/10.3389/fneur.2021.625698>
- Gamma Entrainment Binds Higher-Order Brain Regions and Offers Neuroprotection. (2019). *Neuron*, 102(5), 929–943.e8.
- Götz, J., Bodea, L.-G., & Goedert, M. (2018). Rodent models for Alzheimer disease. *Nature Reviews Neuroscience*, 19(10), 583–598.
- Iaccarino, H. F., Singer, A. C., Martorell, A. J., Rudenko, A., Gao, F., Gillingham, T. Z., Mathys, H., Seo, J., Krtskiy, 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.
- Li, Q., Takeuchi, Y., Wang, J., Gellért, L., Barcsai, L., Pedraza, L. K., Nagy, A. J., Kozák, G., Nakai, S., Kato, S., Kobayashi, K., Ohsawa, M., Horváth, G., Kékesi, G., Lőrincz, M. L., Devinsky, O., Buzsáki, G., & Berényi, A. (2023). Reinstating olfactory bulb-derived limbic gamma oscillations alleviates depression-like behavioral deficits in rodents. *Neuron*, 0(0). <https://doi.org/10.1016/j.neuron.2023.04.013>
- Low-Intensity Focused Ultrasound Pulsation Device Used During Magnetic Resonance Imaging: Evaluation of Magnetic Resonance Imaging-Related Heating at 3 Tesla/128 MHz. (2014). *Neuromodulation: Technology at the Neural Interface*, 17(3), 236–241.
- Manippa, V., Palmisano, A., Filardi, M., Vilella, D., Nitsche, M. A., Rivolta, D., & Logroscino, G. (2022). An update on the use of gamma (multi)sensory stimulation for Alzheimer's disease treatment. *Frontiers in Aging Neuroscience*, 14. <https://doi.org/10.3389/fnagi.2022.1095081>
- McDermott, B., Porter, E., Hughes, D., McGinley, B., Lang, M., O'Halloran, M., & Jones, M. (2018). Gamma Band Neural Stimulation in Humans and the Promise of a New Modality to Prevent and Treat Alzheimer's Disease. *Journal of Alzheimer's Disease: JAD*, 65(2), 363–392.
- Multi-sensory Gamma Stimulation Ameliorates Alzheimer's-Associated Pathology and Improves Cognition. (2019). *Cell*, 177(2), 256–271.e22.
- Optogenetic neuromodulation with gamma oscillation as a new strategy for Alzheimer disease: a narrative review. (2022). *Journal of Yeungnam Medical Science*, 39(4), 269–277.
- Sleep and Alzheimer's disease. (2015). *Sleep Medicine Reviews*, 19, 29–38.
- Yin, L., Li, L., Deng, J., Wang, D., Guo, Y., Zhang, X., Li, H., Zhao, S., Zhong, H., & Dong, H. (2019). Optogenetic/Chemogenetic Activation of GABAergic Neurons in the Ventral Tegmental Area Facilitates General Anesthesia via Projections to the Lateral Hypothalamus in Mice. *Frontiers in Neural Circuits*, 13. <https://doi.org/10.3389/fncir.2019.00073>

