JOHNS HOPKINS
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# Preliminary Effects of 40Hz Auditory Interventions on Sleep and Cognition in Older Adults with Mild Cognitive Impairment

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**Funding :** NIA-R21 AG078917 , the Johns Hopkins Center for Equity in Aging Pilot Fund, and the Johns Hopkins School of Nursing Discovery and Innovation Award.

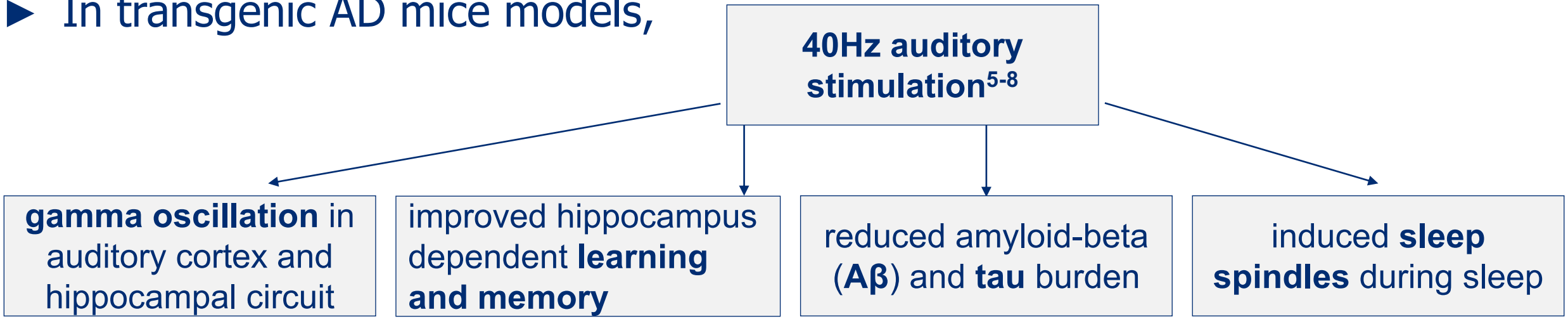
# Outline

- Introduction
- Methods
- Results
- Conclusions

Source Info

# Introduction

- 20% of people aged 60 and above have mild cognitive impairment (MCI).[1,2]
- 1/3 of people living with MCI due to Alzheimer's disease (AD) develop dementia within 5 years, while poor sleep health introduces additional risks.[3,4]
- In transgenic AD mice models,




- 40Hz-Sound has emerged as a potential cognitive enhancement modality for individuals with MCI or AD in some pilot studies.[9-15]

# Introduction

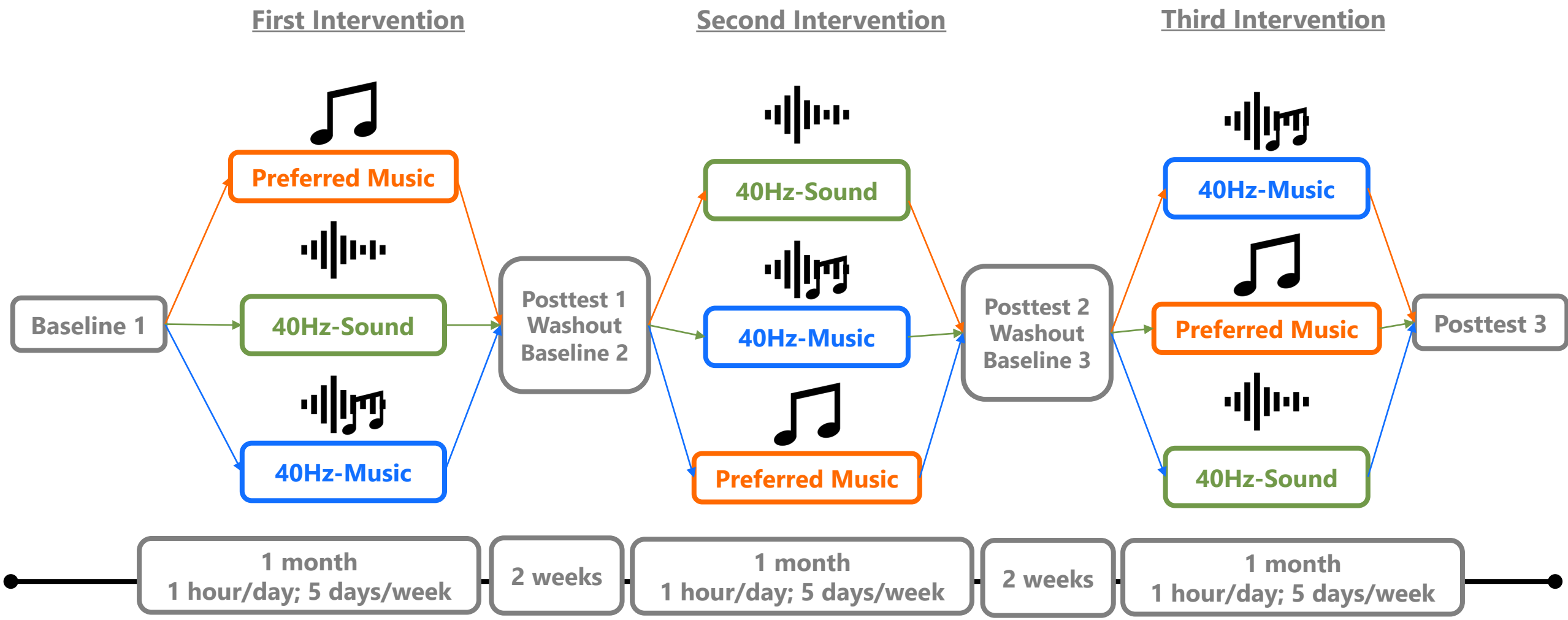
- Both Preferred Music and 40Hz-Sound have shown improved cognitive function among those with cognitive impairment.[16,17]
- However, 40Hz-Sound was often perceived as perturbing or displeasing.[18-20]
- We created a more user-friendly 40Hz modality that combines 40Hz-Sound and Preferred Music → 40Hz-Music


- Aim: To investigate the preliminary efficacy of 40Hz interventions on **sleep** and **cognition** in people with MCI compared to preferred music.

MCI = Mild Cognitive Impairment; AD = Alzheimer's Disease

# Methods

- RCT, crossover design



# Methods

- Measurement
  - Sleep: Pittsburgh Sleep Quality Index (PSQI)
    - 7 sub-domains: Duration of sleep, sleep disturbance, sleep latency, daytime dysfunction due to sleepiness, sleep efficiency, overall sleep quality, and need medications to sleep.
    - Total score
  - Cognition: Cogstate Alzheimer's Battery (CAB)
    - Episodic memory (primary outcome), executive function, attention, and working memory.
    - Global cognitive function (composite score of subdomains)
  - Covariates: Sex, age, and education.

# Methods

- Linear mixed-effect models were utilized to analyze changes in PSQI and cognitive domains among interventions.

$$\text{Changes in PSQI}_{ij} = \beta_0 + \beta_1 \cdot \text{40Hz-Sound}_i + \beta_2 \cdot \text{40Hz-Music}_i + \beta_3 \cdot \text{Sex}_i + \beta_4 \cdot \text{Age}_i + \beta_5 \cdot \text{Education}_i + \beta_6 \cdot \text{Sequence}_i + \text{ID}_j + \epsilon_{ij}$$

$$\text{Changes in Cognition}_{ij} = \beta_0 + \beta_1 \cdot \text{40Hz-Sound}_i + \beta_2 \cdot \text{40Hz-Music}_i + \beta_3 \cdot \text{Sex}_i + \beta_4 \cdot \text{Age}_i + \beta_5 \cdot \text{Education}_i + \beta_6 \cdot \text{Sequence}_i + \text{ID}_j + \epsilon_{ij}$$

i = Type of Intervention; j = Individual; βx = Fix Effect Coefficients; IDj = Random Intercept for Individual

# Results

- Demographics
  - 38 community-dwelling older adults with MCI
  - Age: 68.05 ±7.16 years
  - Sex: 63.16% female
  - Race: 63.16% Black
  - Income: 55.26% financial insecure
  - PSQI Total Score (ranging 0-21) at Baseline 1:
    - Mean(sd): 6.97±4.11
    - 64.1% with sleep disturbance (PSQI>5)

# Results - Sleep

- Compared to Preferred Music, 40Hz-Sound and 40Hz-Music resulted in reduced PSQI total scores (better sleep).

**Between Groups: Changes in PSQI (post-pre) Compared with Preferred Music**

| | PSQI TOTAL | SLEEP DURATION | SLEEP DISTURBANCE | SLEEP LATENCY | DAY DYSFUNCTION[1] | SLEEP EFFICIENCY | OVERALL SLEEP QUALITY | NEED MEDS[1] |
|---|---|---|---|---|---|---|---|---|
| **(Intercept) A: Preferred Music** | -0.28 (-13.37, 12.80) | 2.19 (-4.14, 8.52) | 1.50 (-15.85, 18.84) | 2.29 (-1.44, 6.01) | | -24.95 (-131.92, 82.01) | 1.22 (-1.53, 3.98) | |
| **B: 40Hz Sound** | **-2.13 (-4.29, 0.02)** | -0.17 (-1.19, 0.85) | -2.70 * (-5.39, -0.02) | -0.46 (-1.00, 0.08) | 0.53 (0.14, 1.96) | -7.48 (-25.43, 10.47) | 0.21 (-0.23, 0.65) | 0.22 * (0.05, 0.98) |
| **C: 40Hz + Music** | **-1.61 (-3.48, 0.26)** | -0.07 (-1.04, 0.89) | -1.59 (-4.11, 0.94) | -0.50 (-1.01, 0.01) | 0.97 (0.29, 3.24) | -5.77 (-22.32, 10.78) | 0.18 (-0.22, 0.58) | 0.32 (0.08, 1.25) |
| **Interpretation** | Lower better | Higher better | Lower better | Lower better | Lower better | Higher better | Lower better | Lower better |

* $p<0.05$; [1] Odds Ratio

# Results - Cognition

- Compared to Music, 40Hz-Sound and 40Hz-Music improved episodic memory, as well as similar trends in other domains.

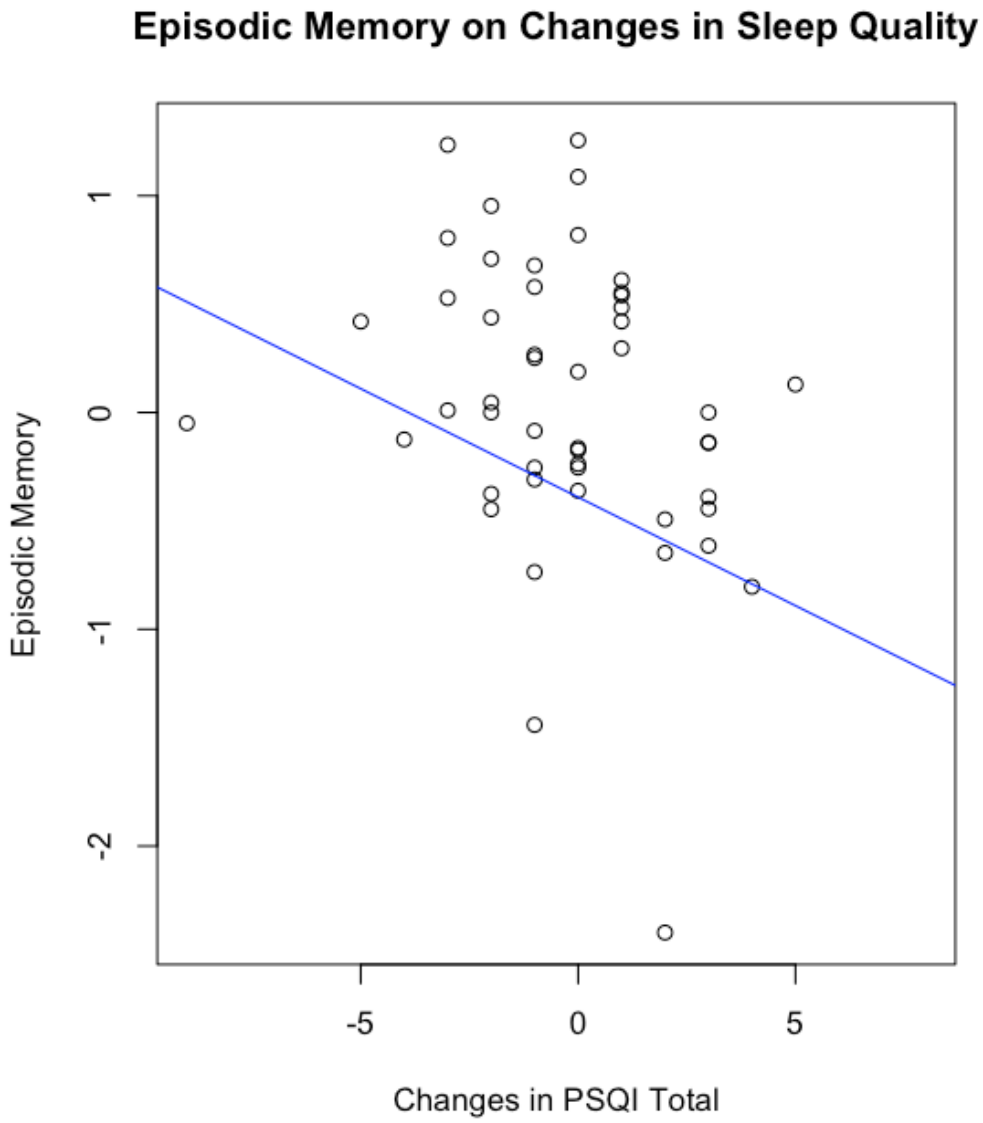
**Between Groups: Changes in Cognitive Domains (post-pre) Compared with Preferred Music**

| | Episodic Memory | Global Cognition | Executive Function | Attention | Working Memory |
|---|---|---|---|---|---|
| **(Intercept) A: Preferred Music** | -0.87 (-2.84, 1.09) | 0.55 (-0.92, 2.02) | -0.85 (-5.95, 4.25) | 1.26 (-1.57, 4.09) | -1.68 (-5.25, 1.89) |
| **B: 40Hz Sound** | **0.33 (-0.03, 0.69)** | **0.28 * (0.01, 0.56)** | 0.25 (-0.42, 0.92) | -0.13 (-0.66, 0.40) | 0.11 (-0.56, 0.78) |
| **C: 40Hz + Music** | **0.38 * (0.05, 0.71)** | **0.27 * (0.03, 0.52)** | 0.55 (-0.04, 1.15) | -0.19 (-0.67, 0.28) | 0.01 (-0.59, 0.61) |

* $p<0.05$

# Results

- A significant association between changes in PSQI and episodic memory (β = -0.10, 95% CI [-0.17, -0.03]) across interventions was identified.



# Conclusion

- 40 Hz auditory interventions hold promise for improving sleep quality and cognitive function in people with MCI.
- A future efficacy trial is needed to test the effects of 40Hz interventions in larger samples of older adults with MCI.

# Reference


1. Kim JG, Kim H, Hwang J, et al. Differentiating amnestic from non-amnestic mild cognitive impairment subtypes using graph theoretical measures of electroen- cephalography. Sci Rep. 2022;12(1):6219. https://doi.org/10.1038/s41598-022- 10322-9.
2. Petersen RC, Lopez O, Armstrong MJ, et al. Practice guideline update summary: mild cognitive impairment. Neurology. 2018;90(3):126–135. https://doi.org/ 10.1212/WNL.0000000000004826.
3. Davis M, O Connell T, Johnson S, et al. Estimating Alzheimer's disease progression rates from normal cognition through mild cognitive impairment and stages of dementia. Curr Alzheimer Res. 2018;15(8):777–788. 10.2174/ 1567205015666180119092427 10.2174/1567205015666180119092427 .
4. Casagrande M, Forte G, Favieri F, Corbo I. Sleep quality and aging: A systematic review on healthy older people, mild cognitive impairment and Alzheimer's disease. International journal of environmental research and public health. 2022 Jul 11;19(14):8457.
5. Iaccarino HF, Singer AC, Martorell AJ, et al. Gamma frequency entrainment attenu- ates amyloid load and modifies microglia. Nature. 2016;540(7632):230–235. https://doi.org/10.1038/nature20587.
6. Martorell AJ, Paulson AL, Suk HJ, et al. Multi-sensory gamma stimulation amelio- rates Alzheimer's-associated pathology and improves cognition. Cell. 2019;177 (2):256–271.e22. https://doi.org/10.1016/j.cell.2019.02.014.
7. Liu C, Han T, Xu Z, et al. Modulating gamma oscillations promotes brain connectiv- ity to improve cognitive impairment. Cereb Cortex. 2022;32(12):2644–2656. https://doi.org/10.1093/cercor/bhab371.
8. Thankachan S, Katsuki F, McKenna JT, Yang C, Shukla C, Deisseroth K, Uygun DS, Strecker RE, Brown RE, McNally JM, Basheer R. Thalamic reticular nucleus parvalbumin neurons regulate sleep spindles and electrophysiological aspects of schizophrenia in mice. Scientific reports. 2019 Mar 5;9(1):3607.
9. Clements-Cortes A, Ahonen H, Evans M, Freedman M, Bartel L. Short-term effects of rhythmic sensory stimulation in Alzheimer's disease: an exploratory pilot study. J Alzheimers Dis. 2016;52(2):651–660. https://doi.org/10.3233/JAD-160081.
10. Cimenser A, Hempel E, Travers T, et al. Sensory-evoked 40-Hz gamma oscillation improves sleep and daily living activities in Alzheimer's disease patients. Front Syst Neurosci. 2021;15: 746859. https://doi.org/10.3389/fnsys.2021.746859.
11. Chan D, Suk HJ, Jackson BL, et al. Gamma frequency sensory stimulation in mild probable Alzheimer's dementia patients: Results of feasibility and pilot studies. PLOS ONE. 2022;17(12): e0278412. https://doi.org/10.1371/journal.pone.0278412.
12. Manippa V, Palmisano A, Filardi M, et al. An update on the use of gamma (multi) sensory stimulation for Alzheimer's disease treatment. Front Aging Neurosci. 2022;14: 1095081. https://doi.org/10.3389/fnagi.2022.1095081.
13. He Q, Colon-Motas KM, Pybus AF, et al. A feasibility trial of gamma sensory flicker for patients with prodromal Alzheimer's disease. Alzheimers Dement (N Y). 2021;7 (1):e12178. https://doi.org/10.1002/trc2.12178.
14. Moretti DV, Frisoni GB, Fracassi C, et al. MCI patients' EEGs show group differences between those who progress and those who do not progress to AD. Neurobiol Aging. 2011;32(4):563–571. https://doi.org/10.1016/j.neurobiolaging.2009.04.003.
15. Musaeus CS, Nielsen MS, Musaeus JS, Høgh P. Electroencephalographic cross-fre- quency coupling as a sign of disease progression in patients with mild cognitive impairment: a pilot study. Front Neurosci. 2020;14:790. https://doi.org/10.3389/ fnins.2020.00790.
16. Ito E, Nouchi R, Dinet J, Cheng CH, Husebø BS. The effect of music-based interven- tion on general cognitive and executive functions, and episodic memory in people with mild cognitive impairment and dementia: a systematic review and meta- analysis of recent randomized controlled trials. Healthcare. 2022;10(8):1462. https://doi.org/10.3390/healthcare10081462.
17. Lam HL, Li WTV, Laher I, Wong RY. Effects of music therapy on patients with dementia—a systematic review. Geriatrics (Basel). 2020;5(4):62. https://doi.org/ 10.3390/geriatrics5040062.
18. Olem D, Sharp KM, MO Johnson. Challenges with engaging participants in behav- ioral intervention research trials. OAJCT. 2009;1(Default):17–21. https://doi.org/ 10.2147/OAJCT.S6841.
19. Weinheimer EA, Chang A, Neubert SW, Wildes JE, Graham AK. Past, current, and future willingness to engage with treatment targets: applying user-centered design to inform the design of a mobile behavioral intervention. Int J Eat Disord. 2020;53(4):611–617. https://doi.org/10.1002/eat.23252.
20. Tichko P, Kim JC, Large E, Loui P. Integrating music-based interventions with gamma-frequency stimulation: implications for healthy ageing. Eur J Neurosci. 2022;55(11-12):3303–3323. https://doi.org/10.1111/ejn.15059.

# Any Questions?