Novel 40 Hz Stimulated Brainwave Display for Reducing the Risk of Alzheimer's Disease

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Abstract

This study used a display as a light stimulus for 40 Hz flicker, assessing the effects on Alzheimer's cognitive function through mouse experiments and human EEG feedback. Results indicate significant improvements in sleep quality and cognitive abilities, supporting 40 Hz stimulation as a treatment strategy.

Author Keywords

Alzheimer's disease; AD; 40 Hz stimulation; Flicker; EEG; Electroencephalogram

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative condition primarily characterized by dementia. Key pathological features include the accumulation of extracellular amyloid-beta (Aβ) plaques, intracellular hyperphosphorylated tau protein, and the formation of neurofibrillary tangles [1]. Clinical symptoms typically involve cognitive deficits and progressive memory loss. Additionally, AD is associated with disruptions in neuronal network oscillations [2], particularly in the gamma frequency band (30-80 Hz), which correlates with cognitive functions such as attention and memory [3-6].

In 2016, Tsai et al. reported a non-invasive 40 Hz light flicker protocol that significantly reduced levels of $A\beta_{1-40}$ and $A\beta_{1-42}$ in the visual cortex of pre-depositing mice, alleviating plaque burden in aging mice [7-8]. This study highlighted the importance of gamma rhythms in engaging neuronal and glial responses to reduce AD-related pathology. Non-invasive 40 Hz light flicker is usually produced using LED lights, however, the treatment duration of up to one hour might lead to discomfort. Therefore, we considered using a monitor as the stimulus source and are committed to developing a more comfortable 40 Hz light flicker stimulation.

In this study, we utilized a 120 Hz LCD to generate non-invasive 40 Hz light flicker stimulation, validating this design by assessing the induced responses in both mice and humans. Control experiments were also conducted to generate flickers at 20 Hz and 30 Hz for corresponding EEG signal detection. Results indicated that all light flickers successfully induced EEG signals, and the intensity of these signals was proportional to the flicker values of the 40 Hz stimulation. We believe that this light stimulation technology using LCDs has potential for improving preventative strategies against Alzheimer's disease in humans.

2. Implementation of Stimulations on Displays and Feedback Detection of Brain Response

To generate 40 Hz light flicker, we utilize a 120 Hz LCD. This involves using three frames with varying luminance levels, as shown in Fig. 1(c): Frame 1 at high luminance, Frame 2 at medium luminance, and Frame 3 at low luminance. Different orders of these levels, such as high-medium-low (HML), can also produce 40 Hz flicker. For 20 Hz flickers in Fig. 1(a), we employ six frames with three distinct luminance levels: Frame 1 and 2 set to high brightness, Frame 3 and 4 to medium brightness, and Frame 5 and 6 to low brightness. In Fig. 1(b), 30 Hz flickers are achieved with four frames: Frame 1 and 2 are high luminance, while Frame 3 and 4 are low luminance. Notably, the integrated brightness of all stimuli aligns with the brightness of the L128 gray tone.

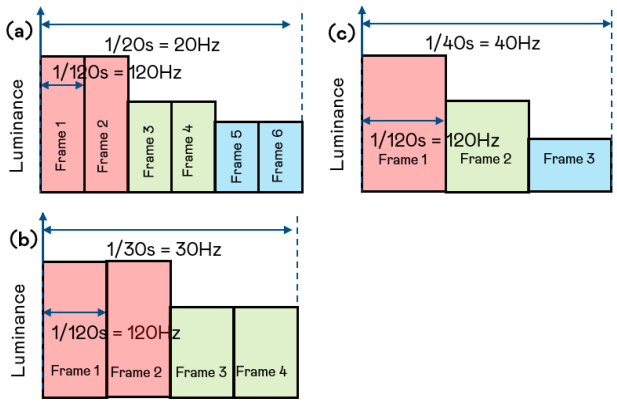

Figure 1. The schematic diagram of (a) 20Hz, (b) 30Hz and (c) 40Hz light-flicker stimulation.

Electroencephalography (EEG) records the brain's spontaneous electrical activity, reflecting postsynaptic potentials of pyramidal neurons in the neocortex and allocortex. A healthy EEG shows activity patterns related to wakefulness, typically in the 1 to 30 Hz frequency range, with amplitudes from 20 to 100 μV. Frequencies are categorized into alpha (8–13 Hz), beta (13–30 Hz), delta (0.5–4 Hz), and theta (4–7 Hz) [3].

3. Experimental Condition

In this experimental design, the verification process is divided into three phases: short-term animal experiments, long-term animal experiments, and EEG response testing following visual stimulation in human subjects.

We collaborated with KYLAB at National Yang Ming Chiao Tung University (NYCU) to conduct a series of animal experiments using a 120 Hz LCD display that cycled through three frames of varying brightness, as illustrated in Fig. 1(c), as stimulus light source to study the effects of 40 Hz light stimulation on cognitive function in Alzheimer's disease. The subjects included wild-type mice (WT) and Alzheimer's disease mouse models (APP/PS1, hereafter referred to as AD mice). At 32 weeks of age, the subjects underwent implantation of physiological signal sensors (EEG, EMG, ECG), followed by a two-week recovery before starting experiments at 34 weeks.

The short-term stimulation experiment aimed to identify effective stimulation conditions, including no light stimulation (No Stim), variable frequency flicker (Random), 40 Hz white light flicker (WL), 40 Hz monochromatic flicker (ISF), and two types of 40 Hz watermark flicker (AUO1, AUO2). This phase lasted two weeks, each light stimulation session lasted one hour and was

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administered one hour prior to the mice's sleep period, and the sleep structures of the mice were evaluated after the stimulation. The long-term stimulation experiment lasted three weeks, repeating the short-term experiment's stimulation conditions, including no light stimulation (No Stim), variable frequency flicker (Random), 40 Hz white light flicker (WL), and 40 Hz watermark flicker (AUO), which refers to AUO2 mentioned in the earlier short-term experiment. Each mouse received one hour of light stimulation daily. Following a two-week stimulation period, cognitive behavioral tests were conducted over the course of one week.

We used adhesive electrodes on the mastoid bone (as a reference electrode) and the visual cortex to collect EEG signals. It is essential that these electrodes be placed on opposite sides of the body, as shown in Fig. 2(a), as EEG signals represent a vector potential [3]. The signals were amplified 2000 times and filtered between 0.34 and 53 Hz using an LTA analyzer (KYLAB), with a sampling frequency of 125 Hz. Frequency analysis was conducted using the Fast Fourier Transform method, categorizing EEG bands into beta (14-32 Hz), alpha (8-14 Hz), theta (4-8 Hz), and delta (0.5-3 Hz). The percentage of the alpha band was calculated as the ratio of total frequency power to alpha band power.

We used a 17.3-inch Full HD LCD screen with a 120 Hz sub-frame rate to induce light flicker at frequencies of 20 Hz, 30 Hz, and 40 Hz, avoiding 60 Hz to prevent interference from alternating current. As depicted in Fig. 3(c), the distance between the subject and the monitor was kept at about 60 cm. Subjects closed their eyes for 1 minute before 6 minutes of light flicker stimulation with their eyes open. To reduce visual fatigue, a 15-minute rest period was implemented between different stimulation conditions.

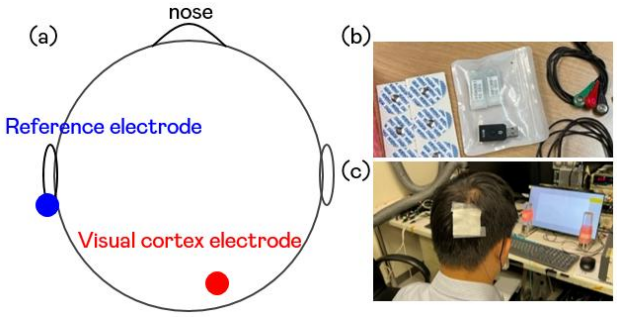

Figure 2. (a) The reference and visual cortex electrode position. (b) The adhesive electrode and (c) experimental setup.

4. Experimental Results

The short-term light stimulation experiment showed that in the first hour of the sleep cycle, normal mice receiving 40 Hz watermark light stimulation (AUO2) exhibited a significant reduction in awake state (AW) and an increase in quiet sleep (QS) duration, as shown in Fig. 3(a)-(b). This indicates quicker sleep onset and longer quiet sleep, which is beneficial for cognitive health. In Alzheimer's disease mice, those receiving the same stimulation demonstrated a longer duration of paradoxical sleep (PS), as seen in Fig. 3(c), which is associated with memory consolidation. These results suggest that 40 Hz light stimulation helps improve sleep quality and cognitive function in both normal and AD mice.

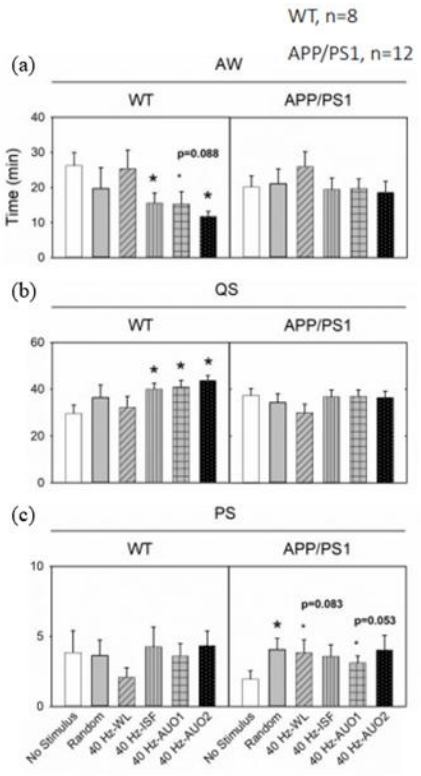

Figure 3. Sleep structure of mice during the first hour of the sleep cycle in the short-term animal experiment: (a) Active Waking; (b) Quiet Sleep; (c) Paradoxical Sleep.

In the long-term animal experiments, we used the Morris Water Maze to assess cognitive behavior. Mice were placed in a fixed-size circular pool with a small platform. As mice instinctively swim to escape water, they learned the platform's location over several days of training. After the platform was removed, we recorded the time it took for the mice to find it, enabling us to evaluate spatial reference memory mediated by the hippocampus.

As shown in Fig. 4, AD mice exposed to 40 Hz white light (WL) stimulation significantly improved their platform search time on the second training day, nearing the performance of normal control mice. In subsequent training days, their times continued to approach the fastest in the group. AD mice receiving 40 Hz watermark light stimulation (AUO) also showed the shortest duration in locating the platform on the first day, with a consistent decrease in time over the following days. After five training days, we removed the platform and measured the time spent in the quadrant where it had been, illustrated in Fig. 5(a), along with the number of passes through that area in Fig. 5(b). Results showed that AD mice receiving 40 Hz watermark stimulation (AUO) excelled in both metrics. These findings indicate that 40 Hz light stimulation effectively enhances cognitive and memory functions in AD mice.

In summary, we used a 40 Hz flickering LCD screen as the stimulus light source. The short-term experiments showed that this light improved sleep quality in both normal and Alzheimer's disease mice. In the long-term experiments, daily one-hour sessions of 40 Hz light stimulation over three weeks significantly enhanced memory and cognitive functions in Alzheimer's disease mice. These results confirm the effectiveness of the 40 Hz display light source in ameliorating Alzheimer's disease effects.

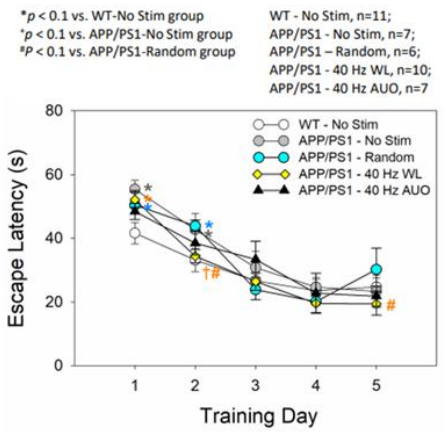

Figure 4. Statistical analysis of escape times for mice during the early training phase of the Morris Water Maze experiment.

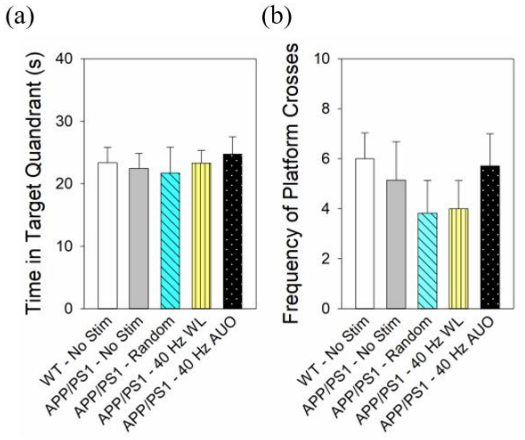

Figure 5. Results from the later testing phase of the Morris Water Maze experiment: (a) Time spent by mice in the original platform quadrant; (b) Frequency of passes through the original location of the platform.

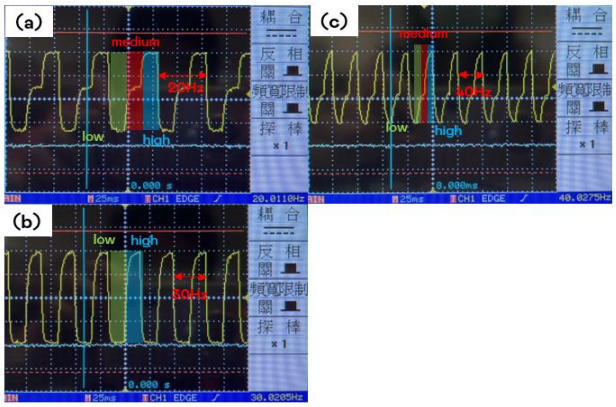

Figure 6. The measured waveform of the (a) 20Hz, (b) 30Hz and (c) 40Hz stimulation by the oscilloscope.

Waveforms for all stimulation types were collected using an oscilloscope (GW Instek GDS-2104). Fig. 6 (a)-(c) displays the measured waveforms for 20 Hz, 30 Hz, and 40 Hz light stimulation at L128. The 20 Hz flicker uses a six-frame mode with three distinct luminance levels. The 30 Hz flicker utilizes four frames with two luminance settings, while the 40 Hz flicker is generated with three frames at three luminance levels. All waveforms met our expectations.

Fig. 7 (a)-(c) shows the power spectral density of the EEG under 20 Hz, 30 Hz, and 40 Hz stimulation. During 20 Hz stimulation, a strong EEG signal is detected immediately after the subjects open their eyes. The relatively weak signal at 40 Hz results from second-order signal effects [3]. Clear EEG signals are also observed during 30 Hz and 40 Hz stimulation, indicating that different frequencies generate corresponding EEG signals. The strong 60 Hz signal in the EEG is attributed to alternating current from the power supply.

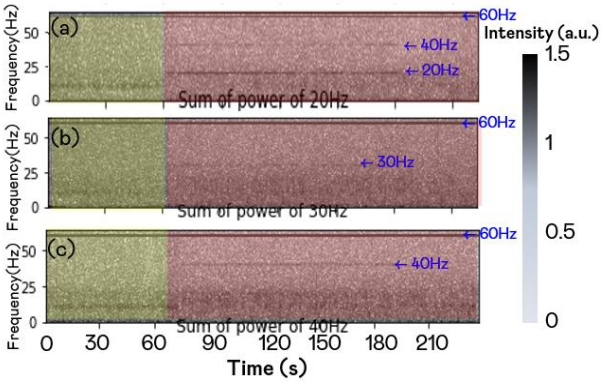

Figure 7. The power spectral density of the EEG under the (a) 20Hz, (b) 30Hz and (c) 40Hz stimulation.

To analyze the difference between rest and stimulation times, we extracted the EEG signal for 40 Hz stimulation from Fig. 7 (c). Fig. 8 shows the EEG signal intensity at 40 Hz. We calculated the average intensity during rest and stimulation periods and defined delta as equation (1). A delta value exceeding 0.1 indicates effective EEG signaling from light stimulation, while a value below 0.1 suggests insufficient stimulation.

$$\text{Delta} = Average_{stimulation} - Average_{rest} \qquad (1)$$

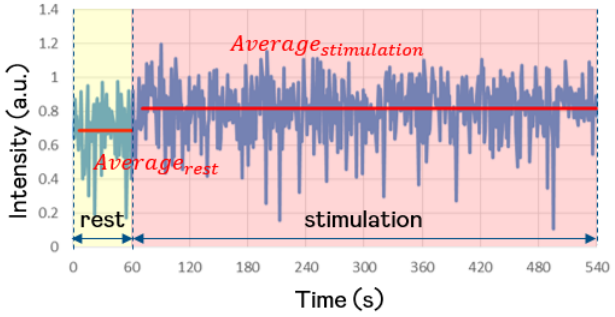

Figure 8. The intensity of the EEG signal in 40 Hz.

To confirm the relationship between the intensity of 40 Hz light-flicker stimulation and the delta value, we varied the ratio of high and low luminance to create four distinct flicker types, defined by the equation:

$$\text{Flicker} = \frac{Luminance_{high} - Luminance_{low}}{Luminance_{average}} \qquad (2)$$

Fig. 9 shows the correlation between delta value and flicker intensity, with recorded delta values of 0.216, 0.321, 0.335, and

0.368 at stimulation conditions of 19.5%, 21.7%, 24.6%, and 27.4% for the 40 Hz light flicker. As expected, the delta value is directly proportional to flicker intensity, indicating that strong 40 Hz stimulation generates significant delta values. However, high intensity may cause discomfort for some individuals. Our future research will focus on finding comfortable and effective parameters for 40 Hz light-flicker stimulation, as this technique shows promise in alleviating the effects of Alzheimer's disease and improving the quality of life for the elderly.

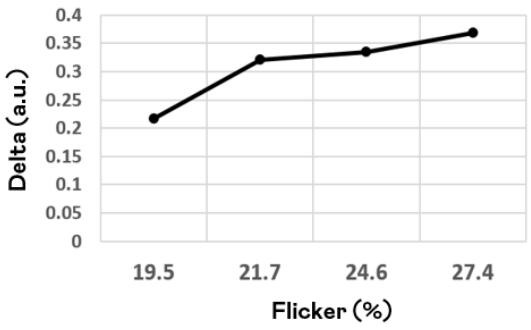

Figure 9. The trend of the delta value and flicker.

5. Conclusion

In summary, we utilized a 40 Hz flickering LCD screen as a stimulus light source, which improved sleep quality in both normal and Alzheimer's disease mice during short-term experiments. Long-term experiments demonstrated that one hour of daily 40 Hz light stimulation for three weeks significantly enhanced memory and cognitive functions in Alzheimer's disease mice, validating the effectiveness of the 40 Hz display light for improving Alzheimer's outcomes. Additionally, we used a 120 Hz LCD to induce 20 Hz, 30 Hz, and 40 Hz stimulations, generating corresponding EEG signals from the human brain. We found that a delta value greater than 0.1 indicates effective light stimulation, while a value below 0.1 signifies invalid stimulation. The recorded delta values for 40 Hz light flicker at intensities of 19.5%, 21.7%, 24.6%, and 27.4% were 0.216, 0.321, 0.335, and 0.368, respectively, showing a proportional relationship with flicker intensity. We believe this technique has the potential to mitigate the harmful effects of Alzheimer's disease.

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