Acousto-optic stimuli to promote coherent 40-Hz frequency entrainment effect

Estímulos acústico-ópticos para promover efeito de arrastamento de frequência coerente de 40 Hz

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Abstract

Background Research has shown that a fundamental frequency of 40 Hz in continuous neural oscillation is indicative of normal brain activity; in Alzheimer disease (AD) patients, these oscillations either disappear or are significantly interrupted. Research has also indicated that the degenerative impacts of AD in mice were mitigated by the synchronization of 40-Hz acousto-optic stimulation (AOS).

Objective To examine the impact of employing a 40-Hz AOS intervention on the induction of a substantial 40-Hz frequency entrainment and improvement in working memory performance among a sample of young individuals in good health. We conduct an analysis of event-related potentials (ERPs) derived from electroencephalogram (EEG) data following the presentation of AOS.

Methods We recruited 20 healthy volunteers (median age: 25 years; 8 female subjects). Following the administration of various stimuli, including no stimuli, 40-Hz AOS, pink noise, and 40Hz acoustic stimuli (AS), the participants were required to complete a working memory task. A total of 62 electrodes were used to record EEG data, which was subsequently analyzed to investigate the impact of AOS on the activity of working memory. We also aimed to determine if AOS lead to a more pronounced 40-Hz frequency entrainment.

Results Following the administration of AOS, a notable enhancement in the 40-Hz power of pertinent cerebral areas was observed, accompanied by a substantial improvement in the performance of the subjects on working memory tests subsequent to the stimulation.

Conclusion The findings unequivocally establish the efficacy of using AOS to enhance the 40-Hz power and working memory.

Keywords
- Alzheimer Disease
- Electroencephalography
- Memory, Short-Term

Resumo

Antecedentes A pesquisa mostrou que uma frequência fundamental de 40 Hz em oscilação neural contínua é indicativa de atividade cerebral normal. Em pacientes com doença de Alzheimer (DA), essas oscilações desaparecem ou são significativamente

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interrompidas. A pesquisa também indicou que os impactos degenerativos da DA em camundongos foram mitigados pela sincronização da estimulação acústico-óptica (EAO) de 40 Hz.

Objetivo Examinar o impacto do emprego de uma intervenção EAO de 40 Hz na indução de um arrastamento substancial de frequência de 40 Hz e na melhoria do desempenho da memória de trabalho entre uma amostra de jovens com boa saúde. Conduzimos uma análise de potenciais relacionados a eventos (PREs) derivados de dados de eletroencefalograma (EEG) após a apresentação de EAO.

Métodos Recrutamos 20 voluntários saudáveis (idade média: 25 anos; 8 mulheres). Após a administração de vários estímulos, incluindo nenhum estímulo, EAO de 40 Hz, ruído rosa e estímulos acústicos (EA) de 40 Hz, os participantes foram obrigados a completar uma tarefa de memória de trabalho. Um total de 62 eletrodos foram utilizados para registrar dados de EEG, que foram posteriormente analisados. para investigar o impacto do AOS na atividade da memória de trabalho. Também pretendemos determinar se o AOS leva a um arrastamento de frequência de 40 Hz mais pronunciado.

Resultados Após a administração de AOS, foi observado um aumento notável na potência de 40 Hz de áreas cerebrais pertinentes, acompanhado por uma melhoria substancial no desempenho dos sujeitos em testes de memória de trabalho subsequentes à estimulação.

Conclusão Os resultados estabelecem inequivocamente a eficácia do uso do AOS para melhorar a potência de 40 Hz e a memória de trabalho.

Palvras-chave
- Doença de Alzheimer
- Eletroencefalografia
- Memória de Curto Prazo

INTRODUCTION

Based on the findings of the "World Alzheimer Report 2018," a new case of dementia occurs approximately every 3 seconds on a global scale. The global population of individuals diagnosed with dementia is estimated to be of approximately 50 million, a figure that has been projected to increase to 150 million by 2050, with 60% to 70% of this population composed of AD patients.

Furthermore, along with the primary clinical characteristics of AD there is also a reported disruption in the oscillation of the neural network.[1] Research[2] has indicated that there are alterations in the gamma band (30 Hz to 80 Hz) oscillations associated with cognitive processes such as attention and memory in individuals diagnosed with Ad. Similar changes have also been observed in mouse models of the disease.[3,4]

While pharmaceutical interventions have demonstrated the ability to provide temporary relief from the symptoms associated with AD, it is important to note that a cure for the condition is currently unavailable.[5,6] As research continues to progress and broaden, there is a growing fascination among individuals with non-pharmacological treatments, particularly those that involve the modulation of brain oscillations.[7,8] Research revealed a synchronization between the internal neural oscillation and external inputs, such as light, sound, and transcranial electrical stimulation.[9,10] External rhythmic stimulation has the potential of entraining the frequency and timing of the oscillation.[11] Research[12] has shown that a fundamental frequency of 40 Hz in continuous neural oscillation is indicative of normal brain activity; this frequency has been associated with an involvement in attentional processes and the functioning of memory.[13] The therapeutic approach of nerve oscillation control is promising due to its potential benefits to individuals with AD and other affected populations.[14]

Motivated by the findings made by Chan et al.,[15] Adaikkan and Tsai,[16] and He et al.,[17] the present work investigated the application of non-invasive acousto-optic stimulation (AOS) to improve the synchronization of brain oscillations at a frequency of 40 Hz. Research[18,19] has indicated that the gamma band has a preference for memory retrieval in familiar situations, and the middle gamma band is activated to regulate the process of recall. Jones et al.[20] reported that, when patients are subjected to sonic stimulation at a frequency of 40 Hz, a broader spectrum of gamma brain oscillations is triggered in comparison to treatment at other frequencies within the gamma band. The administration of acoustic stimulation has been observed[17] to decrease the expression of a relatively ineffective activator of tumor necrosis factor-related apoptosis; this modulation of gene expression has been found to have an impact on neural activity and subsequently enhance cognitive performance in AD patients. The use of AOS results in the induction of more synchronized gamma oscillations, which have a more extensive and profound impact on various brain regions compared to the isolated use of acoustic or optical stimulation.[21] In an electroencephalography (EEG) investigation, Fatemi et al.[22] observed that the application of 40 Hz AOS resulted in a notable improvement in the power spectral density of neural oscillations in the frontal and occipital lobes, and this stimulation technique was able to induce

gamma-frequency entrainment in deeper brain regions, as well as an increase in theta-gamma phase-amplitude coupling. In a functional magnetic resonance imaging (fMRI) investigation, the authors observed that acoustic stimulation at a frequency of 40 Hz resulted in a delay in brain atrophy. Additionally, this stimulation was found to enhance the functional connectivity between the entire brain and the medial visual network, as well as between the posterior cingulate cortex and the precuneus. The aforementioned findings collectively demonstrate that a frequency of 40 Hz is the optimal choice to decelerate or mitigate neurodegenerative processes, and to improve cognitive function through the induction of gamma oscillations.

METHODS

Participants

For the present study, we recruited 20 (8 female and 12 male) subjects with a mean age 25 years. Prior to the commencement of the study, all participants underwent a basic oral assessment to ensure the absence of achromatopsia, color-blindness, and any hearing impairments.

Stimuli

In order to produce a 40-Hz AOS within the gamma frequency range, we developed an auditory signal using the Python programming language; we employed a modulation wave of 40 Hz, which was superimposed on a carrier wave of 250 Hz to serve as the acoustic stimulus. The optic stimuli used was a video in which black and white screens rapidly alternate at a frequency of 40 Hz. We used an image cropping software to seamlessly combine the two stimuli into an AOS.

Visuospatial working memory tasks

To evaluate the potential impact on working memory after the stimulation, the participants were subjected to a sequence of working memory performance tests that lasted either 5 or 8 minutes, with a visual delay matched accordingly. Throughout the entirety of the experiment, the duration of picture presentation in each encoding phase was of 1,500 ms, the retention period lasted for 1,500 ms, and the extraction period spanned 2,000 ms. The time interval between each set of photo test pairs was of 3,000 ms. In all experimental trials there was an equal distribution of target stimuli (50%) and non-target stimuli (50%). The participants were instructed to hit the left arrow key when a match was identified, and the right arrow key when a mismatch was detected. ►**Figure 1** displays examples of the delayed matching-to-sample tasks used in the experiment.

Procedure

The participants were instructed to engage in activities one day before the main experiment, and they were provided detailed information regarding the experimental procedures. It was imperative to mitigate the potential influence of the subjects' learning state on experimental outcomes by ensuring that the experiment commences only after the individuals have transitioned out of this phase.

The EEG signal was susceptible to contamination from noise and the formation of different artifacts, including

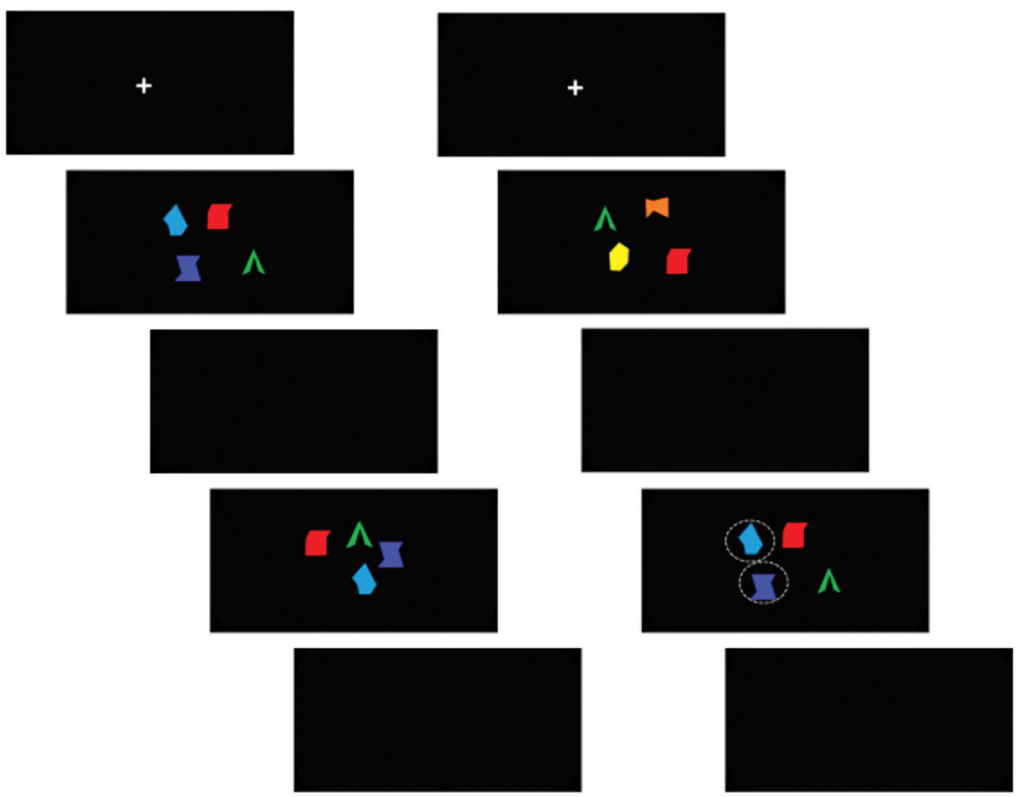

Figure 1 The left is a match, the right is a mismatch; a response was required in the fourth picture.

Stimuli	1)	2)	3)	4)	5)
Experiment content	2 min resting	Visuospatial working memory tasks Pink Noise Stimuli	2 min resting	Visuospatial working memory tasks 40Hz Acoustic Stimuli	2 min resting

Figure 2 The experimental administration of acoustic stimuli.

electromyography artifacts, mains interference, electrocardiogram (ECG) artifacts, and ophthalmic artifacts, due to its high unpredictability and low amplitude. Consequently, the participants were instructed to refrain from performing bodily movements and excessive blinking while undergoing the EEG recording to minimize any interference with the integrity of the EEG data.

The 40-Hz acoustic stimuli experimental session was divided into 5 segments: performance of the first resting EEG (duration: 2 m); working memory task with pink noise stimulation in the control experiment (duration: 5 m); performance of the she second resting EEG (duration: 2 m); working memory task with 40-Hz acoustic stimuli (duration: 5 m); and performance of the third resting EEG (duration: 2 m). The experimental protocol is shown in ►**Figure 2**.

The 40-Hz AOS experimental session was divided into 7 segments: performance of the first resting EEG (duration: 2 m); working memory task after no stimulation in the control experiment (duration: 8 m); performance of the second resting EEG (duration: 2 m); performance of the EEG with 40-Hz AOS (duration: 20 m); performance of the third resting EEG (duration: 2 m); working memory task after the 40-Hz AOS (duration: 8 m); and performance of the fourth resting EEG (duration: 2 m). The experimental protocol is shown in ►**Figure 3**.

Data analyses

Before the processing and analysis of EEG signals, it was important to perform procedures to eliminate interfering noise as follows:

- We identified the channel data;
- We eliminated extraneous data and excluded data segments with significant amplitude fluctuations;
- Filtering: A 50-Hz bandstop filter was used to eliminate power frequency interference, while a bandpass filter ranging from 0.1 Hz to 80 Hz was utilized to recover the desired signals within the target band interval from the EEG data;
- The reference electrode was repositioned to the average value of the left and right mastoids (M1, M2). It was important to note that varying reference sites might significantly influence the experimental outcomes;
- The removal of ocular artifacts and electrical noise was achieved by the application of techniques of independent component analysis (ICA), which is a blind source separation (BSS) algorithm that enables the separation of electrical noise components from the signal, hence facilitating the targeted removal of these specific noise components; and
- We removed the faulty segment.

The present study is on the impact of the operation process of working memory on the activation of the working memory system. To achieve this, we analyzed the task EEG data of the participants while they were engaged in a delayed matching-to-sample working memory task. We specifically examined the characteristics of the event-related potentials (ERPs) during the coding, retention, and decoding periods of working memory. The findings of the present study shed light on the different effects of 40-Hz stimulation on working memory processing across different periods of working memory.

Currently, the prevailing components of ERPs are P1, N1, P2, N170, N2, and P3, among others. These distinct components are regarded as indications of various working memory activities. The prevailing consensus is that P1 represents preattentive and automatic sensory reactions elicited by visual stimuli.[23] The sensitivity of N1 components to

Stimuli	1)	2)	3)	4)	5)	6)	7)
Experiment content	2 min resting	Visuospatial working memory tasks	2 min resting	40Hz Acoustio-Optic Stimuli	2 min resting	Visuospatial working memory tasks	2 min resting

Figure 3 The experimental administration of acousto-optic stimuli.

attention has been noted.[24] The P2 component of the brain's electrical activity has been associated with working memory and classification processes, and its fluctuations are linked to the specific tasks that are being performed.[25] The N170 component is widely recognized as a characteristic feature of face specificity.[26] The N2 component plays a role in the conflict monitoring process that occurs during cognitive control activities.[27]

Several studies have indicated that one of the components of ERPs, known as P3, was linked to various cognitive functions,[28] which include attention resource allocation, working memory renewal, emotional processing, perceptual discrimination, decision-making, information processing, and conflict resolution.[29] These functions are considered indicators of processing ability. Furthermore, the amplitude of P3 has been found to be linked to various factors, including the probability of stimuli, the matching of stimuli, the renewal of working memory, and the readiness of response.[30] Numerous scholars hold the belief that the incubation period of P3 serves as a physiological measure of the time required for stimulation processing.[31] It has been observed that prolonging the duration of low-level sensory processing or high-level classification processing leads to an increase in the incubation period of P3. Conversely, a shorter incubation period results in a more rapid inhibition of external processes, potentially facilitating the transmission of information in working memory.[32] Given the clarity and reliability of the characteristics of the P3 component, as well as its well-established theoretical foundation, the present research aimed to investigate the mechanism through which 40-Hz stimulation affects working memory. We specifically used the amplitude and incubation period of the P3 component as indicators of the task-state EEG signal.

Statistical analyses

The behavioral data obtained from various blocks were subjected to statistical analyses through paired t-tests to examine the impact of AOS on the behavioral performance of working memory.

To assess the impact of various stimuli on working memory, the right rate for each stimulus was computed for all participants. The statistical tests were conducted using repeated-measures analysis of variance (ANOVA) with a significance level of $\alpha = 0.05$. The Mauchly test was conducted to assess the validity of the assumption of sphericity. Additionally, the Greenhouse-Geisser approximation was employed to adjust the degrees of freedom as needed.

RESULTS

ERPs

In contrast to spontaneous EEG, ERPs have considerably diminished amplitudes. The extraction of ERP components from the background noise of EEG involves the superimposition and averaging of numerous EEG waveforms elicited by the identical stimulus. Hence, in the present study, the collection of EEG data for further offline analysis involved the extraction of the initial 200 ms to the final 1,000 ms of the corresponding event marker. Subsequently, a superimposed average was computed.

Based on previous studies in the literature, a seven brain regions were identified as the focal points of investigation: the prefrontal lobe, encompassing the means of Fp1, Fp2, F7, and F8; the frontal lobe, represented by the means of F3, Fz, and F4; the central region, characterized by the means of C3, Cz, and C4; the temporal leaf, represented by the means of T7, T8, P7, and P8; the parietal lobe, encompassing the means of P3, Pz, and P4; the parieto-occipital lobe, represented by the means of PO3, POz, and PO4; and the occipital lobe, encompassing the means of O1 and O2. The group average plot of ERPs in various brain regions of working memory can be created by superimposing and averaging the ERPs of all individuals during the same working memory phase. In the present research, we used the method of superimposed averaging to obtain the ERP waveform associated with working memory.

The P3 components were divided into two groups according to their amplitude and latency: the stimulation group and the control stimulation group. The measurements were taken in the seven brain regions mentioned before. The repeated-measures ANOVA was followed by post-hoc testing to examine simple effects. In instances in which the data failed to satisfy the assumption of sphericity in the hypothesis testing, the Greenhouse-Geisser correction method was employed for adjustment. The findings were analyzed using the Bonferroni correction in the simple effects analysis, with a predetermined statistical significance level of $p < 0.05$.

Statistical values of the P3 component for the coding period of working memory

The mean and standard deviation (SD) values for the amplitude of the P3 components of the acoustic stimuli and AOS obtained in various brain areas are presented in ►**Table 1**.

The repeated-measures ANOVA of the P3 peak amplitude of the acoustic Ssimuli showed that the main effect of group was significant: $F(1, 19) = 31.735$; $p < 0.001$; $\eta_p{}^2 = 0.089$. The amplitude of the P3 component in all brain areas during the presentation of acoustic stimuli was found to be considerably higher compared to the amplitude observed during the presentation of pink noise stimuli. The statistical values were: $F_{prefrontal}\ (1,\ 19) = 12.016$, $p_{prefrontal} = 0.001$; $F_{frontal}\ (1, 19) = 6.973$, $p_{frontal} = 0.009$; $F_{central}\ (1, 19) = 4.504$, $p_{central} = 0.021$; $F_{temporal}\ (1, 19) = 6.403$, $p_{temporal} = 0.012$; $F_{parietal}\ (1, 19) = 4.004$, $p_{parietal} = 0.046$; $F_{parieto\text{-}occipital}\ (1,\ 19) = 7.431$, $p_{parieto\text{-}occipital} = 0.007$; and $F_{occipital}\ (1,\ 19) = 4.082$, $p_{occipital} = 0.044$. The P3 amplitude in the stimulation and control groups presented the greatest magnitude in the prefrontal lobe. Furthermore, the P3 amplitude in the prefrontal lobe showed the most substantial increase subsequent to the administration of acoustic stimuli.

The repeated-measures ANOVA of the P3 peak amplitude of AOS showed that the main effect of group was significant: $F\ (1,\ 19) = 29.070$; $p < 0.001$; $\eta p^2 = 0.070$. The amplitude of the P3 component in all brain areas during the AOS was found

Table 1 Mean P3 amplitudes in 7 brain regions during the coding period of acoustic and acoustic-optic stimuli

P3 amplitudes (μV)	40-Hz acoustic stimuli		Pink noise		40-Hz acoustic-optic stimuli		No stimuli	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Prefrontal	3.007	± 8.191	1.426	± 6.613	2.396	± 8.102	0.727	± 6.371
Frontal	3.989	± 6.408	2.592	± 5.015	1.712	± 7.039	0.254	± 5.194
Central	6.233	± 5.678	5.459	± 4.347	4.329	± 6.491	2.61	± 5.416
Temporal	4.06	± 6.320	2.945	± 4.603	1.414	± 6.410	0.022	± 6.719
Parietal	9.277	± 4.599	7.993	± 3.863	6.325	± 5.317	4.922	± 5.447
Parieto-occipital	8.561	± 5.311	7.176	± 4.120	5.666	± 6.450	4.214	± 6.026
Occipital	5.249	± 3.717	4.852	± 3.767	2.621	± 5.435	2.162	± 5.673

Abbreviation: SD, standard deviation.

to be considerably higher compared to the amplitude under non-Stimuli conditions. The statistical values were: $F_{prefrontal}$ (1, 19) = 27.231, $P_{prefrontal} < 0.001$; $F_{frontal}$ (1, 19) = 12.616, $P_{frontal} = 0.035$; $F_{central}$ (1, 19) = 5.148, $P_{central} = 0.024$; $F_{temporal}$ (1, 19) = 4.503, Ptemporal = 0.034; $F_{parietal}$ (1, 19) = 4.452, $P_{parietal} = 0.038$; $F_{parieto\text{-}occipital}$ (1, 19) = 4.275, $P_{parieto\text{-}occipital} = 0.043$; and $F_{occipital}$ (1, 19) = 3.932, $P_{occipital} = 0.049$. The stimulation and control groups presented the highest amplitude of P3 in the parietal lobe. Furthermore, the amplitude of P3 in the prefrontal lobe showed the greatest increase following the administration of AOS.

Statistical values of the P3 component for the retention period of working memory

The mean and SD values for the amplitude of the P3 components of the acoustic stimuli and AOS obtained in various brain areas are presented in ►**Table 2**.

The repeated-measures ANOVA of the P3 peak amplitude of acoustic stimuli showed that the main effect of group was significant: F (1, 19) = 29.099; $p < 0.001$; $\eta_p{}^2 = 0.083$. The amplitude of the P3 component in all brain areas during the presentation of acoustic stimuli was found to be considerably higher compared to the amplitude observed during the presentation of pink noise stimuli. The statistical values were: $F_{prefrontal}$ (1, 19) = 17.331; $p_{prefrontal} < 0.001$; $F_{frontal}$ (1, 19) = 3.856, $p_{frontal} = 0.041$; $F_{central}$ (1, 19) = 16.215, $p_{central} < 0.001$; $F_{temporal}$ (1, 19) = 3.485, $p_{temporal} = 0.047$; $F_{parietal}$ (1, 19) = 6.182, $p_{parietal} = 0.013$; $F_{parieto\text{-}occipital}$ (1, 19) = 5.427, $p_{parieto\text{-}occipital} = 0.020$; and $F_{occipital}$ (1, 19) = 4.301, $p_{occipital} = 0.033$. The P3 amplitude in the stimulation and control groups presented the greatest magnitude in the prefrontal lobe. Furthermore, the P3 amplitude in the prefrontal lobe showed the most substantial increase subsequent to the administration of acoustic stimuli.

The repeated-measures ANOVA of the P3 peak amplitude of the AOS showed that the main effect of group was significant: F (1, 19) = 7.299; $p < 0.001$; $\eta p^2 = 0.101$. The amplitude of the P3 component in all brain areas during the AOS was found to be considerably higher compared to the amplitude under non-stimuli conditions. The statistical values were: $F_{prefrontal}$ (1, 19) = 27.247, $p_{prefrontal} < 0.001$; $F_{frontal}$ (1, 19) = 4.444, $p_{frontal} = 0.045$; $F_{central}$ (1, 19) = 5.190, $p_{central} = 0.022$; $F_{temporal}$ (1, 19) = 4.961, $p_{temporal} = 0.032$; $F_{parietal}$ (1, 19) = 5.027, $p_{parietal} = 0.026$; $F_{parieto\text{-}occipital}$ (1, 19) = 5.105, $p_{parieto\text{-}occipital} = 0.024$; and $F_{occipital}$ (1, 19) = 4.569, $p_{occipital} = 0.042$. The stimulation and control groups presented the highest amplitude of P3 in the parietal lobe. Furthermore, the amplitude of P3 in the prefrontal lobe presented the greatest increase following the administration of AOS.

Table 2 Mean P3 amplitudes in 7 brain regions during the retention period of acoustic and acoustic-optic s

P3 amplitudes (μV)	40-Hz acoustic stimuli		Pink noise		40-Hz acoustic-optic stimuli		No stimuli	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Prefrontal	5.933	± 5.374	4.562	± 4.639	8.209	± 24.767	6.577	± 23.642
Frontal	3.221	± 4.524	2.055	± 3.962	7.658	± 15.836	6.251	± 13.157
Central	4.069	± 4.417	2.922	± 4.673	3.966	± 9.265	2.544	± 6.464
Temporal	1.126	± 2.972	0.060	± 4.181	1.82	± 8.372	0.646	± 7.321
Parietal	1.857	± 3.767	0.486	± 4.759	2.109	± 6.686	0.644	± 3.547
Parieto-occipital	1.319	± 3.750	0.201	± 4.652	1.645	± 5.384	0.914	± 3.333
Occipital	1.958	± 3.339	0.719	± 4.678	0.505	± 4.468	0.172	± 2.469

Abbreviation: SD, standard deviation.

Statistical values of the P3 component results for the extraction period of working memory

The repeated-measures ANOVA of the P3 peak amplitude of acoustic stimuli showed that the main effect of group was not significant. ($p > 0.05$).

Behavioral data

Mean and SD values were used to quantify the accuracy and reaction time across various stimuli. The statistical analysis of the stimulation and control groups involved the evaluation of the correct rate and reaction time using a paired *t*-test. The findings are presented in ►**Table 3**. The mean accuracy of the stimulation group was found to be greater than that of the control group.

DISCUSSION

Given the substantial body of previous research indicating that AS or AOS interventions have been found to improve working memory, cognitive functioning, attention, and other related factors, it was reasonable to anticipate notable disparities in behavioral performance and EEG features following exposure to AOS in comparison to alternative stimuli. The result was consistent with the anticipated outcome.

ERPs

Following the stimulation, we observed an improvement in working memory capacity, resulting in a corresponding and directly proportional increase in P3 amplitude.

After the completion of an attentional-orienting exercise, the participants presented an improvement in the allocation of cognitive resources towards various tasks. Moreover, the allocation of attention specifically pertaining to the processing of target stimuli was heightened during the process of constructing representations. During the coding phase of working memory, we observed that the amplitude of the P3 component presented a greater increase after the administration of AOS. This finding suggests that the use of AOS facilitated the allocation of additional cognitive resources towards task performance. Furthermore, the improvement in attention allocation associated with target processing was evident during the encoding of representations. The retention period is the only phase of working memory in which external stimuli are absent, and the sole objective for the participants was to concentrate on the internal execution of the supplied items. The P3 component observed during this stage typically signifies the initiation of the memory maintenance process, evaluation of stimulation, and the ability to inhibit interference. As the stage progresses, a higher amplitude of P3 may indicate a greater inclination to suppress irrelevant interference and sustain attention to successfully accomplish the task of memory consolidation. Additional research has demonstrated that the allocation of attention resources by the central executive system of working memory is influenced by the overall level of arousal. The overall level of arousal plays a crucial role in determining the processing capacity available for attention allocation during ongoing tasks. Moreover, individuals with lower cognitive abilities exhibit a reduction in the amplitude of the P3 component. The present study examines the impact of auditory stimulation on the P3 amplitude during the encoding and retention periods. The findings suggest that there was a higher increase in P3 amplitude following auditory stimulation at 40 Hz, which may be attributed to the heightened level of arousal induced by the frequency. This heightened arousal level was believed to assist the attention allocation process, hence improving processing ability.

Research[33,34] on P3 components in different areas if the brain has consistently demonstrated that the parietal lobe is typically associated with P3 activation. Research on metabolism[33] has indicated that the parietal lobe frequently takes on a significant role in the allocation of attention throughout space and the cognitive processing of spatial relationships. Numerous studies[34] have provided empirical evidence supporting the involvement of the parietal cortex in encoding stimuli throughout a range of visual working memory tasks. This observation suggests that, regardless of the specific stimulus employed, the coding period consistently elicited the highest P3 amplitude inside the parietal lobe, as indicated by the findings of the present investigation.

Behavioral data

A notable disparity in the precision of the outcomes of working memory tasks was observed between the stimulation and control groups. The accuracy after the administration of AOS was notably greater compared to what it was after

Table 3 Accuracy and reaction time under different stimuli

Stimuli	Accuracy			Reaction time		
	Mean	SD	*t*-test	Mean	SD	*t*-test
WS	0.684	0.128	$t = 3.684$	1278.969	895.228	$t = -1.945$
OS	0.807	0.095	$p = 0.002^*$	1196.150	817.861	$p = 0.052$
PN	0.677	0.211	$t = 2.843$	1051.315	512.897	$t = -0.713$
AS	0.786	0.113	$p = 0.011^*$	1032.506	439.874	$p = 0.476$
No stimuli	0.754	0.161	$t = 3.285$	1005.605	469.029	$t = -1.756$
AOS	0.857	0.079	$p = 0.004^*$	958.893	490.147	$p = 0.080$

Abbreviations: AOS, acoustic-optic Stimuli; AS, acoustic stimuli; OS, optic stimuli; PN, pink noise; SD, standard deviation; WS, white-screen stimuli.

Table 4 Comparison of the accuracy and reaction time of different stimuli

Stimuli	*t*-test	
	Accuracy	Reaction time
AOS-AS	$t = 2.392$ $p = 0.028^*$	$t = -2.762$ $p = 0.006^*$
AOS-OS	$t = 2.455$ $p = 0.024^*$	$t = -6.232$ $p = 0.000^*$
AS-OS	$t = -0.242$ $p = 0.812$	$t = -4.547$ $p = 0.000^*$

Abbreviations: AOS-AS, comparison between acoustic-optic stimuli and acoustic stimuli; AOS-OS, comparison between acoustic-optic stimuli and optic stimuli; AS-OS, comparison between acoustic stimuli and optic stimuli.

the administration of acoustic or optic stimuli. A substantial reduction in the reaction time was also observed. This finding shows that the administration of 40-Hz AOS can significantly improve the working memory performance and memory capacity of the participants.

In conclusion, the possible mechanisms to improve working memory performance before and after 40-Hz AOS were analyzed from the perspective of the task-state EEG analysis. The results show a significant improvement in accuracy after the administration of 40-Hz AOS, which can be explained by the effectiveness of said stimulation to enhance the performance and cognitive ability of the working memory system.

Authors' Contributions

XH: conceptualization, data curation, formal analysis, investigation, and writing of the original draft; LW: supervision and writing – review and editing; SY: funding acquisition.

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Conflict of Interest

The authors have no conflict of interest to declare.

References

1 Palop JJ, Mucke L. Network abnormalities and interneuron dysfunction in Alzheimer disease. Nat Rev Neurosci 2016;17(12):777–792
2 Wang J, Fang Y, Wang X, Yang H, Yu X, Wang H. Enhanced Gamma Activity and Cross-Frequency Interaction of Resting-State Electroencephalographic Oscillations in Patients with Alzheimer's Disease. Front Aging Neurosci 2017;9(July):243
3 Gillespie AK, Jones EA, Lin YH, et al. Apolipoprotein E4 Causes Age-Dependent Disruption of Slow Gamma Oscillations during Hippocampal Sharp-Wave Ripples. Neuron 2016;90(04):740–751
4 Iaccarino HF, Singer AC, Martorell AJ, et al. Gamma frequency entrainment attenuates amyloid load and modifies microglia. Nature 2016;540(7632):230–235
5 Dos Santos Picanco LC, Ozela PF, de Fatima de Brito Brito M, et al. Alzheimer's Disease: A Review from the Pathophysiology to Diagnosis, New Perspectives for Pharmacological Treatment. Curr Med Chem 2018;25(26):3141–3159
6 Folch J, Ettcheto M, Petrov D, et al. Review of the advances in treatment for Alzheimer disease: Strategies for combating β-amyloid protein. Neurología (Engl Ed) 2018;33(01):47–58(English Edition)
7 Kastanenka KV, Hou SS, Shakerdge N, et al. Optogenetic Restoration of Disrupted Slow Oscillations Halts Amyloid Deposition and Restores Calcium Homeostasis in an Animal Model of Alzheimer's Disease. PLoS One 2017;12(01):e0170275
8 Martinez-Losa M, Tracy TE, Ma K, et al. Nav1.1-Overexpressing Interneuron Transplants Restore Brain Rhythms and Cognition in a Mouse Model of Alzheimer's Disease. Neuron 2018;98(01):75–89.e5
9 da Silva VF, Ribeiro AP, Dos Santos VA, Nardi AE, King AL, Calomeni MR. Stimulation by Light and Sound: Therapeutics Effects in Humans. Systematic Review. Clin Pract Epidemiol Ment Health 2015;11(01):150–154
10 Herrmann CS, Rach S, Neuling T, Strüber D. Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. Front Hum Neurosci 2013;7:279–279
11 Calderone DJ, Lakatos P, Butler PD, Castellanos FX. Entrainment of neural oscillations as a modifiable substrate of attention. Trends Cogn Sci 2014;18(06):300–309
12 Herrmann CS, Demiralp T. Human EEG gamma oscillations in neuropsychiatric disorders. Clin Neurophysiol 2005;116(12):2719–2733
13 Belluscio MA, Mizuseki K, Schmidt R, Kempter R, Buzsáki G. Cross-frequency phase-phase coupling between θ and γ oscillations in the hippocampus. J Neurosci 2012;32(02):423–435
14 McDermott B, Porter E, Hughes D, et al. Gamma Band Neural Stimulation in Humans and the Promise of a New Modality to Prevent and Treat Alzheimer's Disease. J Alzheimers Dis 2018;65(02):363–392
15 Chan D, Suk HJ, Jackson BL, et al. Gamma Frequency Sensory Stimulation in Probable Mild Alzheimer's Dementia Patients: Results of a Preliminary Clinical Trial[J]. Social Science Electronic Publishing; 2021
16 Adaikkan C, Tsai LH. Gamma Entrainment: Impact on Neurocircuits, Glia, and Therapeutic Opportunities. Trends Neurosci 2020;43(01):24–41
17 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(01):e12178
18 Mably AJ, Colgin LL. Gamma oscillations in cognitive disorders. Curr Opin Neurobiol 2018;52:182–187
19 Dvorak D, Radwan B, Sparks FT, Talbot ZN, Fenton AA. Control of recollection by slow gamma dominating mid-frequency gamma in hippocampus CA1. PLoS Biol 2018;16(01):e2003354
20 Jones M, McDermott B, Oliveira BL, et al. Gamma Band Light Stimulation in Human Case Studies: Groundwork for Potential Alzheimer's Disease Treatment. J Alzheimers Dis 2019;70(01):171–185
21 Suk HJ, Chan D, Jackson B, et al. Sensory gamma frequency stimulation in cognitively healthy and AD individuals safely induces highly coordinated 40 Hz neural oscillation: A preliminary study of non-invasive sensory stimulation for treating Alzheimer's disease. Alzheimers Dement 2020;16(S7):e041146
22 Fatemi SN, Sedghizadeh MJ, Aghajan H. Theta-gamma phase-amplitude coupling explains the advantage of auditory plus visual gamma entrainment in Alzheimer's therapy. Alzheimers Dement 2022;17(S7):e053451

23 Bozhilova N, Kuntsi J, Rubia K, Michelini G, Asherson P. Electrophysiological modulation of sensory and attentional processes during mind wandering in attention-deficit/hyperactivity disorder. Neuroimage Clin 2021;29(04): 102547
24 Arjona-Valladares A, Fondevila-Estévez S, Fernández-Linsenbarth I, et al. Event-related potentials associated to N-back test performance in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2021;111:110347
25 Turtola ZP, Covey TJ. Working memory training impacts neural activity during untrained cognitive tasks in people with multiple sclerosis. Exp Neurol 2021;335:113487
26 Sun T, Li L, Xu Y, et al. Electrophysiological evidence for women superiority on unfamiliar face processing. Neurosci Res 2017; 115:44–53
27 Polich J. Updating P300: an integrative theory of P3a and P3b. Clin Neurophysiol 2007;118(10):2128–2148
28 Ortega R, López V, Carrasco X, et al. Neurocognitive mechanisms underlying working memory encoding and retrieval in Attention-Deficit/Hyperactivity Disorder. Sci Rep 2020;10 (01):7771
29 Sahin L, Figueiro MG. Flickering red-light stimulus for promoting coherent 40hz neural oscillation: a feasibility study. J Alzheimers Dis 2020;75(03):911–921
30 Callahan-Flintoft C, Wyble B. Non-singleton colors are not attended faster than categories, but they are encoded faster: A combined approach of behavior, modeling and ERPs. Vision Res 2017;140:106–119
31 Schubert AL, Hagemann D, Frischkorn GT, Herpertz SC. Faster, but not smarter: An experimental analysis of the relationship between mental speed and mental abilities. Intelligence 2018;71:66–75
32 Donchin E, Coles MGH. Is the P300 component a manifestation of context updating? Behav Brain Sci 1988;11(03):357–374
33 Zacks J, Rypma B, Gabrieli JD, Tversky B, Glover GH. Imagined transformations of bodies: an fMRI investigation. Neuropsychologia 1999;37(09):1029–1040
34 Jonides J, Lacey SC, Nee DE. Processes of working memory in mind and brain. Curr Dir Psychol Sci 2005;14(01):2–5