Original Article

The Investigation of Simultaneous EEG and Eye Tracking Characteristics During Fixation Task in Mild Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder that occurs many years before the first clinical symptoms. Finding more exact, significant, and valuable criteria or indices for the diagnosis of the mild form of Alzheimer's disease is very important for clinical and research purposes. Electroencephalography (EEG) and eye tracking biomarkers would provide noninvasive tools for the early detection of AD. Due to the advantages of EEG and eye tracking, in this study, we employed them simultaneously to conduct research on the mild AD. For this purpose, 19 patients with mild AD were compared with 19 gender- and age-matched normal subjects who did not have any history of cognitive or neurological disorders. EEG and eye-tracking data were concurrently collected in both groups in a fixation task. Our results revealed that the total fixation duration was significantly shorter for the AD patients, but their fixation frequency was more than that of the controls. In addition, increased theta power and decreased alpha power were observed in the AD group. Interestingly, there was a statistically significant correlation between fixation frequency and alpha power in the parietal area in the control group. However, this connection was not statistically significant in the AD group. The findings also indicated an elevated coherence in the AD patients in the parieto-occipital area. It is assumed that the AD patients might use the neural compensational processes for the fixation state. This study provides evidence for the simultaneously EEG and eye-tracking changes in the areas, which are involved in the control of the fixational eye movements.

Keywords

Alzheimer's disease, coherence, EEG, eye tracking, fixation

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Introduction

Among the causes of dementia, the most common brain degenerative disease is Alzheimer's disease (AD). Some studies indicate that this may be due to the degeneration of synapses and neuronal death in the brain regions, such as the hippocampus, the entorhinal cortex, and the neocortex. This usually results in impaired cognitive, memory, judgment, and even language and functional skills.[1,2] Researchers believe that the number of people with the age-related diseases, such as AD, will dramatically increase over the next few years due to a falling birth rate and an increase in the world's elderly population. This shows the necessity develop tools and techniques for early diagnosis of AD.[3]

Electroencephalography (EEG) has been shown to be a reliable tool for the research and diagnosis of dementia. EEG characterization of AD has been carried out by many researchers. EEG helps in the differential diagnosis and the prediction of disease progression.[4,5] It has been specified that the EEG neurobiomarkers in AD patients include the changes in the power spectrum in lower frequencies,[6] and a reduction in the coherence of fast rhythms.[6-8] Generally, EEG signals of AD patients illustrate increased power in the slow frequency range (theta and delta) and decreased power in the higher

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frequencies (alpha and beta) in the resting state,[9] as well as reduced coherence in alpha and beta bands, compared with normal subjects.[8,10] In addition, it has been shown that the synchrony of EEG in AD patients reduces in alpha, beta, and gamma frequency bands using global field synchronization and the synchronization likelihood was significantly reduced in the 14- to 18- and 18- to 22-Hz bands in the AD groups compared with controls.[11,12] In addition, recent studies have shown that spectral analysis can be used to diagnose AD from other types of dementia.[5,13-15] These studies employed different EEG markers such as spectral power and coherence in all EEG bands, which are valuable for group classification.[16-19] Recently, the interest in analyzing EEG rhythms as noninvasive markers for the neurophysiological evaluation of patients with AD has increased, in order to make clinical decisions during the disease progression.[10,20,21]

Moreover, the simplicity of the tools needed to collect the required quantitative information is very important. Eye-tracking technology, is rapidly developing for use in future research.[22,23] There are numerous potential benefits for using eye tracking criteria to study cognitive visual processing in AD patients. Compared with many traditional neurophysiological evaluations, eye movement recordings do not require additional behavioral responses such as pressing buttons or verbal responses to assess cognitive changes.[24] Eye-tracking metrics are often used to study more complex cognitive functions, especially in cognitive psychology.[25,26] Investigations have shown that there have been some eye movement disorders in AD patients compared with control subjects. That is, longer saccade latency in the prosaccade task and lower accuracy in the antisaccade task have been observed in AD patients.[27-29] Using a visual paired-comparison task, the researchers examined eye movement parameters such as the number of fixations and the fixation duration in mild cognitive impairment (MCI) patients to detect short-term memory problems.[30] MCI is usually present before the development of Alzheimer's stage, and this mostly develops into AD.[31] Fixation is the ability to keep the eyes on a target for a prolonged period.[32] When the fixation point is present, the fixation cells are activated and the movement cells are inhibited. Frontal eye field (FEF) and posterior parietal cortex seem to play important roles in the production of volitional saccades and fixation escapements.[33,34] Saccadic eye movements are produced by activating the saccade neurons and inhibiting the fixation neurons in the superior colliculus.[35,36] The disappearance of the fixation point reduces the activation of the fixation cells, and inhibition is removed from the movement cells. Thus, with the decrease in the activity of the fixation cells, the reaction time of the saccadic eye movements reduces.[35] However, almost nothing is known about the neurological systems that are associated with the fixation process. In addition, changes in fixation values associated with Mini-Mental State Evaluation (MMSE) scores were observed in AD. These results showed that the fixation studies might be beneficial for detecting AD progress[37,38]; however, this issue has not been adequately studied in AD patients.

According to clinical experience regarding to some confusing overlaps between symptoms of mild AD other types of dementia, there is no definitive diagnostic tool for differential diagnosis and early detection of mild AD cases. This highlights the importance of identifying a useful biomarker. As mentioned, EEG and eye tracking biomarkers are profitable in research and diagnosis of AD. Accordingly, our goal is to analyze the features of eye movements, especially fixation, by combining EEG and eye tracking recordings and exploring the relationship between them in patients involving to the early stages of AD. Specifically our aim is to describe that how the neurological activity and connectivity, as well as the characteristics of eye tracking in AD patients, are modulated in comparison with normal subjects.

Methods

Study Population

Twenty-one patients with mild AD (age = 59 $\pm$ 2.7 years; 8 male and 11 female) were recruited from the 17 Shahrivar hospital (Mashhad, Iran). Two of them were not included in the analyses because perform the experiment correctly. As a result, the final sample consisted of 19 patients with mild AD. A control group was also set up, including 19 subjects without any history of cognitive, neurological, or psychiatric disorders and of similar gender and age range (age= 58 $\pm$ 2.4 years; 9 male and 10 female). All participants sat through the same neurological assessments and cognitive tests. Meanwhile, all subjects were right-handed according to Edinburgh Handedness Questionnaire. Both groups started the experiment by filling out the medical history and mood questionnaires. A neurologist visited AD patients and they underwent complete clinical tests such as brain neuroimaging (computed tomography or magnetic resonance imaging) and neuropsychological interview. Moreover, the patients were asked to answer a set of standard questionnaires, including MMSE,[39] Geriatric Depression Scale (GDS),[40] and clinical dementia rate (CDR)[41] to confirm the diagnosis and to exclude other causes of dementia, as well as to have clinically homogeneous groups. The final diagnosis was based on a consensus meeting where all the available clinical data and the results of the ancillary investigations were considered. A diagnosis of probable AD was based on the McKhann criteria.[42] Before starting the study, all participants signed an informed consent form according to local biomedical ethics committee rules. The demographic characteristics of the participants including MMSE, CDR, and GDS scores, age, education, and gender are presented in Table 1.

Table 1. Demographic Data.

Characteristics	AD (n = 19), mean (SD)	Control (n = 19), mean (SD)	*P*
Gender, male/female, n	8/11	9/10	—
Age, years	59 (2.7)	58 (2.4)	.09
Education, years	11 (0.9)	11 (0.59)	.12
MMSE	20 (0.9)	28 (1.34)	.00***
CDR	1.1 (0.3)	0 (0.0)	.00***
GDS	2 (0.5)	2 (0.6)	.32

Abbreviations: AD, Alzheimer's disease; CDR, clinical dementia rate; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination.
***Significant at $P < .001$.

Data Collection

EEG and eye-tracking data were concurrently collected in both groups. The EEG system (g.tec Medical Engineering GmbH) and the SMI eye-tracker (Senso Motoric Instruments) were synchronized. Gaze data were recorded with a sample rate of 250 Hz. The eye-tracker was placed in front of the subject (approximately 50 cm), just below a 22-inch flat screen monitor. The stimuli were presented through the SMI Experiment Center (Version 3.7). EEG data were acquired, using a g.USB amp, while the subjects were in a relaxed state with opened eyes and doing the fixation task. The recordings were done in an electromagnetic shield room in dim light. Before beginning the recoding process, 5-point calibration was performed. The participants were instructed to not move and to focus their eyes on a black cross "+" in the center of the white screen and the experimenters were blinded toward group assignment. After the task began, they were instructed to continue looking at the black sign in the middle of the white screen during the whole process (6 trials, 30 seconds each, and the rest interval in between was 30 seconds with closed eyes).

Eye-Tracking Data Analysis

The different values of the fixation task, including fixation frequency (count/s), total fixation duration (ms), and heat map have been measured, using Be Gaze (V. 3.7) software. Heat map shows the areas with many fixations or data samples in warm colors (red) and the regions with less data in cold colors (blue). Statistical analyses were performed using *t* test ($P < .05$).

EEG Data Analysis

Preprocessing. EEG data were acquired from 28 electrodes (FP1, F7, F3, Fz, FC5, FC1, T7, C3, CP5, CP1, P7, P3, O1, FP2, F8, F4, FC6, FC2, T8, C4, Cz, CP6, CP2, P8, P4, Pz,O2,Oz), according to the 10-20 system, with a sampling frequency of 512 Hz. Three electrodes were used to record the electro-oculogram (EOG); 2 electrodes were placed above and below the left eye to record the vertical EOG, and one was positioned at the outer canthus of the left eye to record the horizontal EOG. A band-pass 0.5- to 60-Hz filter was applied to remove the low- and high-frequency artifacts. The EEG data were later re-referenced to the algebraic mean of the left and right mastoids. The artifacts (eg, eye-blinks, eye-movements) were then removed by employing Independent Component Analysis (ICA), using EEGLAB toolbox.[43] Finally, the epochs were excluded if within a moving window of 800 and 200 ms, the standard deviation of the amplitude exceeded 25 μV at any electrode location.

Power spectral estimation. The preprocessed data were imported into custom made MATLAB code for the quantitative EEG analyses. The quantitative features were extracted from each epoch, and their average was calculated for all epochs.[44] Then, the Power Spectrum was estimated, using the Welch method (Hamming window of 3 Hz, 0.5 overlap). In this study, the EEG power was estimated in the 5 sub-bands, including 1 to 4 Hz (delta), 4 to 8 Hz (theta), 8 to 12 Hz (alpha), 12 to 30 Hz (beta), and 30 to 45 Hz (gamma). Finally, to evaluate which areas showed differential features for the AD patients and the healthy controls, we statistically compared all channels across the subjects by a nonparametric cluster-based permutation test,[45,46] using Field-Trip toolbox.[46] The initial threshold for cluster definition was set to $P < .05$. Last, the final significance threshold for summed *t* values within clusters was set to $P < .05$.

Coherence analysis. The functional connectivity index between each pair of electrodes was computed, in 5 sub-bands—1 to 4 Hz (delta), 4 to 8 Hz (theta), 8 to 12 Hz (alpha), 12 to 30 Hz (beta), and 30 to 45 Hz (gamma) separately,[19] through calculating the magnitude of the squared coherence value. The coherence data were, then, represented as a matrix in which the electrodes were displayed on the *x* and *y* axes. The elements of the 28×28 matrix represented the color-coded coherence values between the electrodes. One-way analysis of variance was used to calculate the statistical differences for AD and control group. Generally, $P < .05$ is considered as a significance level.

Correlation analysis. Moreover, a Pearson's correlation analysis was performed to examine the relationship between extracted eye tracking and EEG data. Significant value was $P < .05$.

Results

Eye-Tracking Summary Metrics

The results of the fixation task, including fixation frequency and total fixation duration, are presented in Figure 1A. The AD patients spent significantly less total time to fixate on the target, compared with the healthy controls ($t = -2.39$, $P = .02$). In addition, the patients with AD showed more fixation frequencies ($t = 3.92$, $P = .0003$) compared with the control group. Percentage of fixation time on the target calculated for

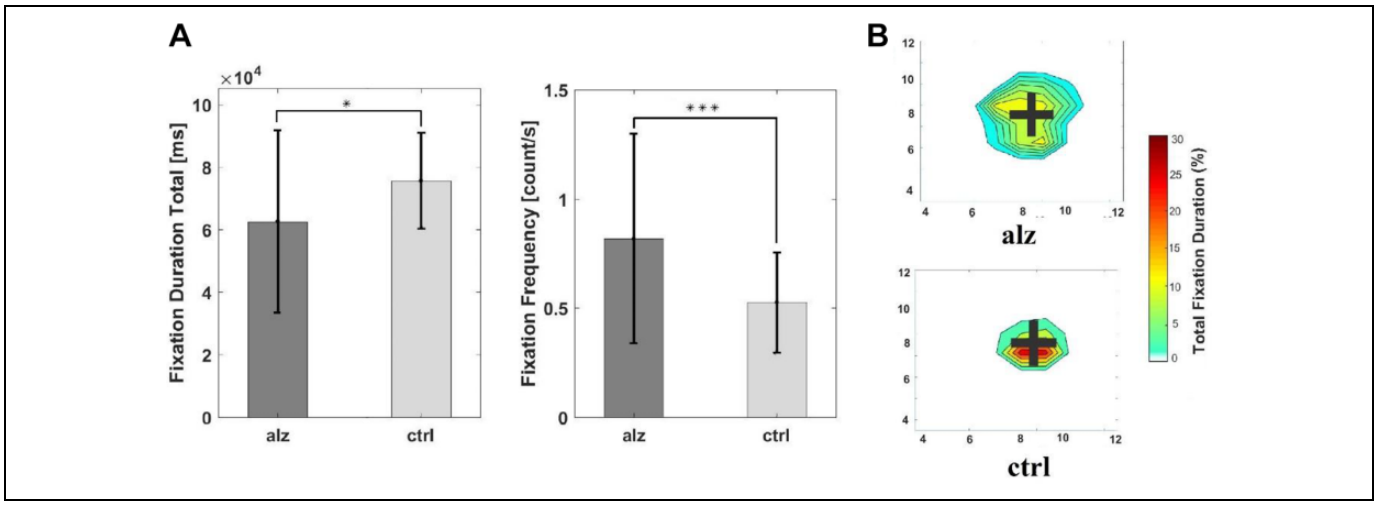

Figure 1. Eye-tracking results. (A) Fixation frequency and the total fixation duration for the Alzheimer's disease (AD) (alz) and control (ctrl) groups. As the figure demonstrates, the frequency of fixation increased ($P = .0003$, $t = 3.92$) and the duration time of fixation decreased ($P = .02$, $t = -2.39$) in the AD patients, compared with the control group. (B) Heat map of the AD group and control group. They indicate the points and time that both groups fixated on the screen. The areas with more fixation time are highlighted with warm colors and the regions with less fixation time are marked with cold colors. As it can be seen, the distribution of the points in the AD group is farther away from the center, that is, the "+" point. It shows that the AD patients spent less time on the central point and they were more fixated around the "+" point.

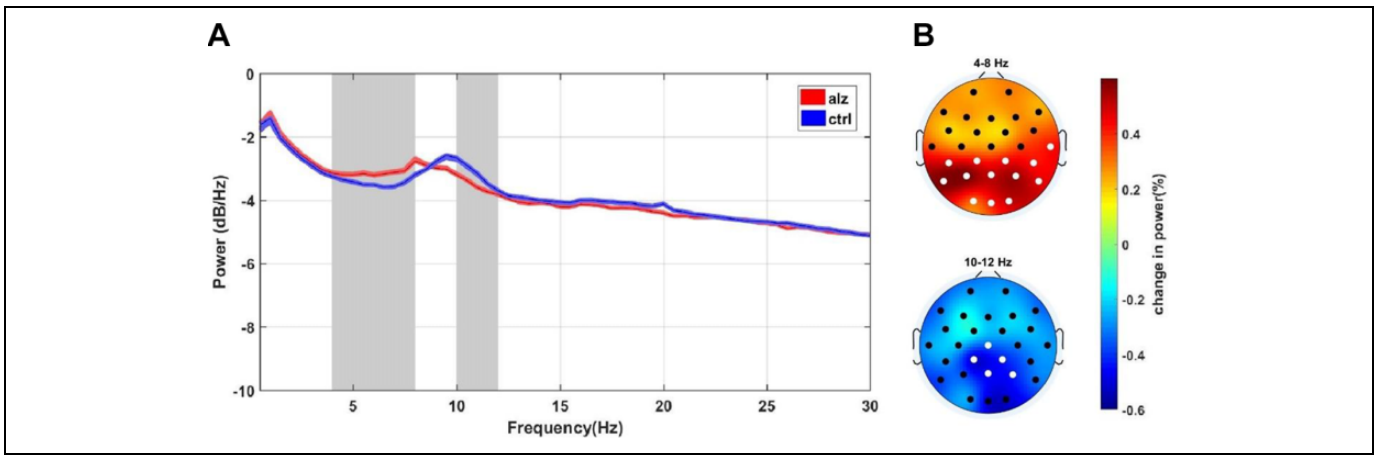

Figure 2. The normalized averaged power spectra of EEG. (A) The power in the theta band of the Alzheimer's disease (AD) group was significantly greater than that of the control group ($P < .05$); however, the alpha power decreased in the AD group compared with that of the control group ($P < .05$), as indicated by the gray-shaded region. (B) Scalp map of the differences in the power of 4 to 8 Hz and the power of 10 to 12 Hz in the AD group compared to the normal one. The clustered significant channels have been demonstrated with the white circles.

both groups. The results showed that control subjects fixated more on the "+" (centralized) point, but the patient group focused more on the points around the + mark and they assigned less time to fixation. These results also confirmed that the distribution of the points in the AD group was farther away from the center and it was more scattered.

Power Results

Figure 2 displays the normalized average spectra logarithms across all channels. Further cluster analysis revealed that there were topographic differences in the alpha and theta power between the 2 groups. Cluster analysis showed that in the parieto-occipital regions, there was an increase in the power in the theta band in the mild AD group compared with the normal group ($P = .01$). On the other hand, the AD group showed a decrease of the alpha power in the parietal area ($P = .04$). However, no significant differences were observed in the delta, beta, or gamma bands.

Furthermore, the Pearson's correlation test revealed a positive correlation between the fixation frequencies and the alpha frequency power in the control group in FC2

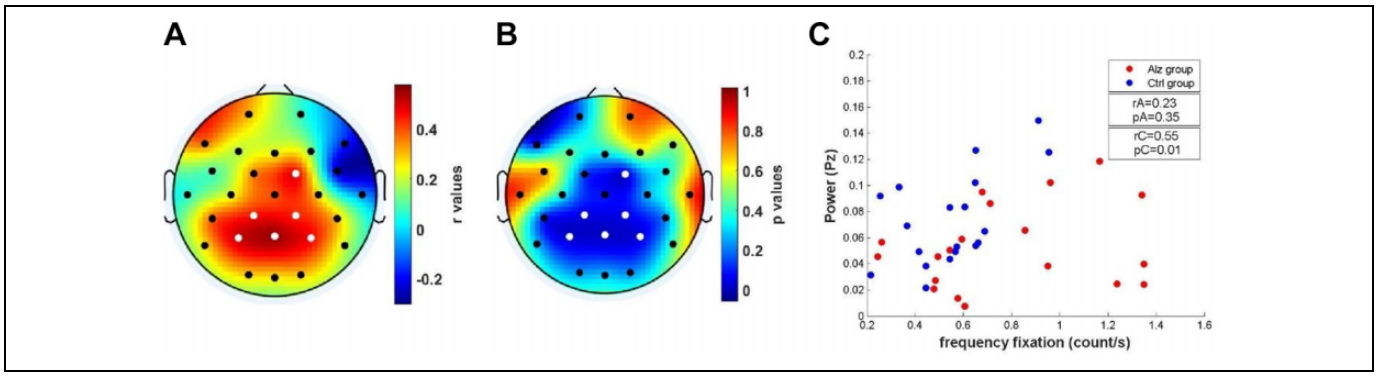

Figure 3. Pearson correlation analysis. (A) The scalp map of *r* values shows the relationship between the fixation frequency and the alpha power in the control group. (B) The scalp map of *P* values is presented for the control group. The channels that showed the same patterns of changes are adjacent to each other in the parietal area of the brain. (C) Scatter plot between the normalized alpha power (8-12 Hz) and the frequency fixation (count/s) in the Pz channel in the Alzheimer's disease (AD) and healthy groups. A statistically significant positive correlation was observed between the fixation frequencies and the alpha frequency power in the control group in FC2 ($P = .04$, $r = 0.47$), CP1 ($P = .05$, $r = 0.45$), P3 ($P = .03$, $r = 0.51$), Pz ($P = .01$, $r = 0.55$), and P4 ($P = .05$, $r = 0.46$); however, this relationship was not statistically significant in the AD group ($P > .05$). Moreover, in the control group, the CP2 channel had a *P* value very close to the significant level ($P = .06$, $r = 0.43$). The significant channels are demonstrated with white circles.

($P = .04$, $r = 0.47$), CP1 ($P = .05$, $r = 0.45$), P3 ($P = .03$, $r = 0.51$), Pz ($P = .01$, $r = 0.55$), and P4 ($P = .05$, $r = 0.46$); nonetheless, this relationship was not observed in the AD group ($P > .05$) (as an example, the scatter plot over the Pz channel is presented in Figure 3). The CP2 channel also had a *P* value very close to the significant level ($P = .06$, $r = 0.43$). In Figure 3A, the scalp map of *r* values and in Figure 3B, *P* values are presented. As it is observed, the channels that have the same pattern around the association between the fixation frequencies and the alpha band power are next to each other in the parietal region of the brain in the healthy group.

Coherence Analysis Results

The coherence matrix for the pairwise electrodes showed more connectivity in the delta, theta, alpha, and beta bands in AD group (Figure 4). The percentages of the coherence changes in the paired channels between the AD and control groups are plotted in Figure 4A. The topographic map of the coherence values also revealed that the most obvious differences in the functional connectivity between the brain regions were observed in the parieto-occipital area (Figure 4B), the same place where the power changes occurred. The coherence values were higher in the AD group compared with those in the control group for the majority of the intra hemispheric long-distance electrode pairs. The largest increase in the coherence ($P < .05$) was observed in the connections between the occipital electrodes and the temporal electrodes as well as the connections between the occipital electrodes and the parietal electrodes.

Discussion

In clinical examinations, the diagnosis of AD from other types of dementia in patients is complex because the symptoms of AD overlap with those of the other types. In addition, AD begins before the onset of clinical symptoms and diagnosis is very important in the early stages of the disease. And there is no certain diagnostic test for Alzheimer's identification. Current methods are simple neurological and physical, blood and cerebrospinal fluid, mental mode and neuropsychological test. In addition, brain imaging techniques such as computed tomography scan, magnetic resonance imaging, and positron emission tomography have developed during recent decades. Considerable results have also been observed in some studies related to EEG and eye-tracking investigations. Our results suggest that EEG recordings during an eye fixation seem to be helpful in diagnosing AD patients. The findings of the current study showed that the total time of fixation significantly decreased for the AD patients, compared with healthy people. Moreover, the AD patients showed more fixation frequencies and their focusing points were farther away from the stimulus and they were more distributed. Additionally, the correlation between fixation and alpha power was not observed in the AD. It might be possible that the areas involved in fixation to be impaired in AD. The previous eye tracking studies have revealed a statistically significant correlation between the cognitive processes and the duration of fixation. Based on these investigations, the longer fixations which were the result of more attention were positively correlated with more concentration.[47,48]

The observed eye movement changes in the AD patients might be plausibly justified by two reasons. First, there might be some impairment in the areas responsible for the control of fixation.[49,50] As Molitor et al[22] indicated, the changes in the eye fixation movements might show damage to the posterior areas of the saccade neural pathway in AD patients. Furthermore, it is stated that supplementary eye field (SEF) controls

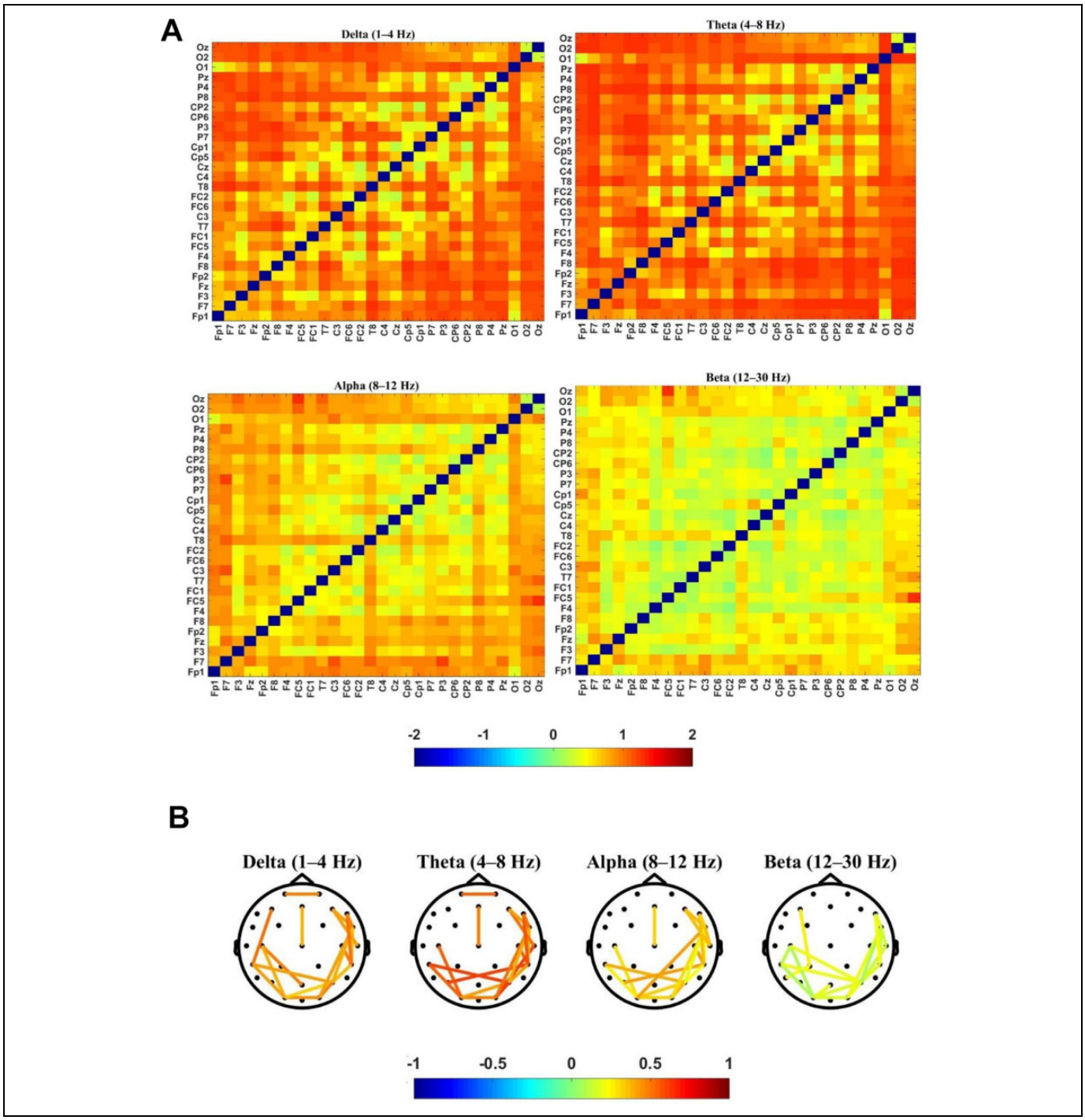

Figure 4. The coherence analysis. (A) Coherence matrix for the pairwise electrodes. The magnitude squared coherence average was calculated for each pairs of channels. The coherence data were represented as a matrix in which the electrodes were displayed on the *x* and *y* axes. The elements of the 28 × 28 matrix represent the color-coded coherence values for the electrodes. (B) The scalp map of the coherence changes presented in percentages. As this figure illustrates, the differences of the coherence values are more in the AD group, compared with the normal one ($P < .05$). The significant connections are shown with the color-coded lines.

eye movements and attention and it plays a role in oculomotor tasks.[51,52] Additionally, the activation of SEF along with inactivity in another eye movement region, such as the FEF, has been seen in fixation duration in text reading tests. Finally, the dorsolateral prefrontal cortex is one of the areas that controls eye movements because it is usually activated in oculomotor

tasks.[53] Additionally, in AD patients some brain areas that are involving in eye movements control show somehow structural and functional changes such as atrophy of parietal, frontal and occipital lobes.[22,24,54,55] Second, the changes in the fixation movements might be due to the cognitive impairments. It has been reported that the movements of eye fixations have been affected by attention and working memory in AD patients.[49]

The findings of the present research also displayed the increased power of the theta band in the parieto-occipital area and the decreased power of the alpha band in the parietal area in the AD group, compared with the normal one. The obtained results are in agreement with those of the previous studies.[9,14,56] However, in some studies, enhanced gamma band power (GBP) in AD was observed when compared with controls.[57] In our results, this increase in GBP in AD was not significant. It seems that beta and gamma changes are shown in the more advanced stages of the disease. Probably for this reason, beta and gamma power changes may not be significant in our research. Previous findings have shown that decreased beta power can be seen in people with AD before changing gamma.[58] It has been shown that there is a close relationship between the increase in the oscillatory power in slow frequencies and the degree of cognitive impairments.[4,59] The elevated slow EEG rhythms are associated with decreased cortical cholinergic activity.[60] The EEG changes can differentiate the AD patients from the patients with other types of dementia. For example, EEG demonstrates the reduction of posterior alpha power that occurs specifically for the mild AD group compared with the vascular dementia group and the normal subjects.[56] Additionally, Moretti et al[61] indicated the decrease in the occipital individual alpha frequency peak in the mild AD in the resting state. Villa et al[62] also demonstrated that the first subcortical and cortical changes in the AD patients were neuronal atrophy. An example of the neuronal atrophy is the fact that the left fronto-parietal connections are heavily influenced by AD pathology during the early stages of the disease.[14] Moreover, QEEG studies have shown that there exists a negative relationship between alpha amplitude, and hippocampal atrophy and the magnitude of the brain gray matter in the MCI and AD patients.[16,20,63] Animal investigations also revealed that the reduction of acetylcholine measurements led to the decreased high-frequency EEG coupling and increased slow frequency coupling.[62] It is assumed that the fast frequencies are produced by the thalamic neural networks and the alpha and beta oscillations are mainly generated in the cortex and then they spread all over intra cortical connections.[58,64] In sum, it is assumed that the correlation between the elevated slow activities and cognitive impairment in the AD patients can be due to the changes of basal forebrain neurons, which, in turn, lead to the deficiency of the cholinergic system in the brain, and finally to memory disturbances and EEG slowing rhythms.[65] Additionally, we examined the correlation between the EEG and Eye tracking results. The findings revealed a positive association between the normalized alpha power and the fixation frequency in the control group in the parietal region. However, it is worthy of note that this relationship was not observed in the AD group. This issue not reported yet and it needs further investigations to discuss the reasons. Some articles stated that many cognitive sections such as perception, encoding, and recognition are related to the alpha oscillations and are guided through attention.[66,67] Moreover, alpha activities play a crucial role in attention so that they support attentional focus processes.[6,68] As mentioned earlier, cognitive impairments including attention disorders have been reported in AD. Therefore, the attention disorders might cause changes in the relationship between the fixation and alpha frequency in the AD group.

The next finding of the study indicated a higher strength of functional connectivity for AD, compared to control. An elevated coherence was observed in the parieto-occipital area in the AD patients. However, the previous results, regarding the study of coherence in AD patients, are controversial. That is, some investigations have reported a decrease in coherence, whereas others have demonstrated an increase in it in AD patients. For instance, Prichep[69] showed that a significant reduction in EEG synchronization in fast rhythms was associated with decreased MMSE in the MCI and AD patients. In a similar vein, Güntekin et al[19] and Başar et al[18] reported a decreased coherence in the AD subjects, compared with normal elders. Nonetheless, Başar et al[21] revealed an increased coherence in the gamma band in the AD patients, compared to the controls. Because of the fact that the functional connectivity methods were more depend on changes in electrophysiological characteristics, these differences could be due to differences in recording mode, recording techniques, and analysis methods.

The underlying reasons for changes in coherence could be cortico-cortical uncoupling as well as decreased synaptic coupling.[70] The intra cortical connections are necessary for neural interactions, but these connections are modulated in AD patients. Accordingly, functional connectivity may be a useful biomarker for the early diagnosis of AD[71] and coherence is one of the methods of examining functional connectivity.[10] In the current study, we observed that the coherence increased in the mild AD group in the delta, theta, alpha, and beta bands. It might be possible that the reason for this phenomenon is the fact that the AD patients were likely to use neural compensation to encode data. That is, the brain tried to recruit the alternative structures that were not normally used, to compensate for the brain damage.[72-74] Several studies have shown that the unwonted neuronal oscillations in the AD patients were associated with the synaptic compensation processes.[75-77] Additionally, a series of investigations have examined the neural compensation mechanisms.[17,78-80] For instance, Bajo et al[17] reported an elevated inter hemispheric connectivity in the MCI patients; he proposed that the results could reflect a compensatory mechanism. The compensatory mechanism occurs as follows: It has been said that multimodal

information processing is changed in cortico-cortical connections. That is why "disconnection syndrome" has been proposed for AD.[81] Disabled local compensation leads to a rapid decrease of network dynamics in the theta and alpha bands[82]; this, in turn, leads to the increase in coherence. The last issue about functional connectivity is the fact that the most increase of connectivity in AD functional brain networks has been observed in the long-distance connections.[83] The same was true for our results. That is, the increased functional connectivity in the intra cortical long-distance connections was significant. This finding might indicate that the AD patients employed the neural compensational processes for the fixation state.

Conclusions

In conclusion, interestingly, all our results reported the changes in the parietal and parieto-occipital regions in the AD patients. It seems that these regions are involved in the control of the fixational eye movements. Therefore, the observed changes in fixation in AD patients might be due to changes in the areas of eye movement control in the early stages of the disease. This could characterize the combination of EEG with eye-tracking tools might be effectual in diagnosing and prediction of AD in the early stages of disease. However, little research has been done on AD, using changes in eye movements. Further research is needed to obtain better conclusions and greater understanding of the neural processing of fixation.

Author Contributions

Malihe Moghadami contributed to acquisition, analysis, interpretation and drafted manuscript. Sahar Moghimi contributed to analysis and revised manuscript. Ali Moghimi contributed to conception, design, interpretation, and gave final approval. Gholamreza Malekzadeh contributed to design and acquisition. Javad salehi Fadardi contributed to design and revised manuscript.

Declaration of Conflicting Interests

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