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Correlations of frontal resting-state EEG markers with MMSE scores in patients with Alzheimer's disease

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Abstract

Background: A previous study suggests that resting-state EEG biomarkers measured at prefrontal region (Fp1, and Fp2) are moderately correlated with Mini-Mental State Examination (MMSE) scores of elderly people with Alzheimer's disease. In this study, our objective was to investigate whether resting-state EEG biomarkers recorded from frontal region are correlated with each MMSE sub-scores. 20 elderly patients diagnosed as Alzheimer's disease entered to the study. After completion of MMSE, subjects underwent EEG for 5 min with closed eyes condition. We measured median frequency, theta/alpha power ratio, and relative powers. To examine the relationship between these features and MMSE sub-scores first, Pearson correlation coefficients were computed for each feature and MMSE sub-scores. Then, *p* values were computed for each correlation. Finally, a Bonferroni correction was done.

Results: Nine correlations have been found for markers recorded from F3, F7, and Fz. Alpha and beta relative powers were the markers which shows correlations. We found that MMSE overall, attention, and calculation scores are significantly correlated with beta relative powers recorded from F3, and Fz, and alpha relative power from F7. Orientation to time scores were correlated with F3, and Fz beta relative powers. The only correlation found for orientation to place was beta relative power of F3.

Conclusions: Our results indicate that there are correlations between frontal EEG markers and MMSE sub-scores of patients with Alzheimer's disease. The results show that alpha and beta relative powers are markers correlated with MMSE scores. It seems that if we want to develop predicting models for Alzheimer's disease, using data recorded from other frontal electrodes, especially what we have introduced should be considered.

Keywords: Dementia, Electroencephalography, Alzheimer's disease, Clinical neuroscience

Introduction

Alzheimer's disease (AD) is a growing problem that affects 35% of people over the age of 80 [1]. In 2015, AD was the sixth leading cause of death in the United States [2]. According to the criteria of National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), AD cannot be definitely diagnosed clinically, unless there is a histopathologic evidence. On the other hand, the NINCDS-ADRDA criteria proposes that cases with dementia established by clinical examination and documented by Mini-Mental State Examination (MMSE) can be assigned as "probable" AD patients [3]. MMSE is a short examination for assessment of cognitive abilities and is widely used for diagnosis of dementia in clinical setting. It includes examination of cognitive abilities that are diagnostic and clinically important for patients with AD (i.e., orientation to time and place, attention, calculation abilities, and recall) [4].

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However, tries have been done to make the NINCDS-ADRDA criteria more reliable for researches using biomarkers of AD including Magnetic Resonance Imaging, Positron Emission Tomography, and cerebral fluid analyses [5]. Although resting-state electroencephalography (EEG) has not been yet considered as an approved method for initial evaluation of people with cognitive impairment, it is considered as a potential option for the diagnosis of dementia [6]. It becomes serious especially when we consider that EEG is relatively inexpensive [7].

Advancements in quantitative EEG (qEEG) for characterizing neuropsychiatric diseases have lead to further studies to clarify its diagnostic and prognostic uses in clinical and research setting [8, 9]. Several studies on EEG biomarkers have been done that suggest various correlations with AD presentations. Prinz and Vitiello, in a classic research, proposed that lower alpha rhythm frequency was seen in AD patients compared to control subjects [10]. Prichep et al. found that an increase in theta absolute and relative powers is associated with mild cognitive deterioration, while an increase of powers in delta band is associated to more severe cases [11]. Their findings of absolute power were replicated by Chiaramonti et al., while they also suggested an increase in alpha and beta absolute powers recorded from more anterior regions [12]. Moretti et al. suggested that mild AD patients show lower alpha relative powers than normal subjects [13]. A review on the clinical perspective of EEG in dementia also suggested that EEG biomarkers can help to identify mild cognitive impairments from normal subjects [14].

Recently, several studies have been done on correlations between EEG biomarkers and MMSE scores of patients with dementia. Garn et al. suggest that MMSE scores of 79 probable AD patients are significantly associated with alpha relative power recorded in resting-state [15]. In 2019, Choi et al. found that resting-state EEG biomarkers measured at the prefrontal region (i.e., Fp1, and Fp2) are moderately correlated with MMSE scores. They suggest that finding correlations between EEG biomarkers and MMSE scores can be helpful to develop precise diagnostic and monitoring tools for AD [16]. A 2021 study by Doan et al. was done to identify whether prefrontal biomarkers are appropriate for screening dementia, using correlations between markers and MMSE scores [17].

It can be concluded, to develop tools for prediction of AD, finding strong correlations between EEG biomarkers and each sub-scores of MMSE is worthy. It is suggested that the "orientation to time" score of MMSE is a strong predictor of subsequent cognitive decline [18]. It is also suggested that a decline in calculation abilities is one of the hallmark cognitive features of AD [19, 20]. Recall assessment is also diagnostic in classification of patients with AD, and can be used in detection of mild cognitive impairment [21, 22]. In an overall view, it may be claimed that frontal cortex is dedicated for purposeful mental actions [23, 24], and because the MMSE consists of action-requiring examinations, it seems that the evaluation of frontal markers is an appropriate option to investigate correlations with MMSE scores of patients with AD. In this study, our objective was to investigate whether EEG markers recorded from frontal region are correlated with MMSE scores of patients with AD. For this purpose, we examined data recorded from frontal region.

Methods

Participants

From November 2020 to February 2021, 20 elderly patients referred to the Asayesh Private Clinic diagnosed as AD entered to the study. All subjects were 55 years old or older. After examination, the attending psychiatrists put diagnosis on patients. The assessments and final diagnosis were done by the collaborating psychiatrist. The assessments were based on the current criteria for AD. All patients diagnosed both as dementia according the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), and as probable AD according to the NINCDS–ADRDA criteria [3]. According to these criteria, a patient is diagnosed as probable AD if there are core clinical criteria for dementia, and also special characteristics for probable AD—e.g., insidious onset, clear-cut history of worsening of cognition by report or observation, etc. [25]. All participants were medication-free –i.e., not treated with any medication at least for 3 months. All participants had not any history of stroke and less than 5 h sleeping in the last night before referring to the clinic. All criteria were verified by asking patients' caregivers. Informed consents for entering to the study were taken by caregivers.

MMSE completion

After recording basic demographic information, the participants were examined with the MMSE. A Persian version of the MMSE used for cognitive examination [26]. This version consisted of eight sub-scores that in this study, we used four main sub-scores including Orientation to time (5 scores), Orientation to place (5 scores), Attention and Calculation (17 scores), Recall (3 scores), and altogether as an overall score (30 scores). The process of MMSE completion, including asking questions and recording answers, was conducted by nurses under the supervision of the attending psychiatrist.

EEG recordings

After MMSE completion, Subjects underwent EEG for 5 min with closed eyes condition. The brain activities of subjects were recorded via EEG according to the International 10–20 system using Mitsar 19 channel system [27]. All the EEG electrode contact impedances were maintained below 5 kΩ. To remove interferences from EEG, a high-pass filter with a cut-off frequency of 0.1 Hz, a low-pass filter with a cut-off frequency of 50 Hz, and a Notch filter with cut-off frequencies of 45 and 55 Hz were used. We used Infomax independent component analysis (Infomax ICA) decomposition to remove usual eye movement such as saccades or blinking [28]. Recordings were further cleaned with an automated *z*-score based method, using FASTER plugin [29]. After processing the EEG signal, various features were extracted from it.

EEG markers and computation

In this study, we measured Median Frequency of amplitude distribution of different frequency bands, Theta/Alpha Power Ratio, and Relative Powers. These markers were reported as suitable classification biomarkers for AD [16]. Median that is calculated from median of amplitude distribution of times series of EEG signal at each frequency band including Delta (1–4 Hz), Theta (4–8 Hz), Alpha (8–13 Hz), Beta (15–20 Hz), High-beta (20–30 Hz).

Relative power has been used as a feature to classify the mild cognitive impairment and mild AD patients from age-matched controls [30, 31]. The relative power of each given band/sum of power from 1 to 45 Hz was calculated by below:

$$\mathrm{RP}\left(f_1,f_2\right) = \frac{P(f_1,f_2)}{P(1,45)} \times 100\%$$

Calculation of Relative Powers. $P(x)$ indicates the power, $\mathrm{RP}(x)$ indicates the relative power, and f_1, f_2 indicate the low and high frequency, respectively.

The ratios of power for slow frequency bands in frontal electrode was computed based on absolute powers of theta and alpha frequencies [32]. The recorded relative powers include delta, theta, alpha, beta, and gamma frequency bands. For EEG processing and metric computation, we used MATLAB software version 2019a.

Statistical analysis

For the purpose of this study, we analyzed EEG markers recorded from 7 electrodes consist of Fp1, Fp2, F3, F4, Fz, F7, and F8. EEG markers used in the analysis were 8 consist of delta median frequency, theta median frequency, alpha median frequency, Theta/Alpha power ratio, delta relative power, theta relative power, alpha relative power, and beta relative power. The analysis is conducted using the IBM SPSS software version 26.0.0.0. Pearson correlation coefficients were computed for each marker and MMSE overall score and sub-scores. *p*-values were computed for each correlations, then a Bonferroni correction was done by multiplying all *p*-values by 280 (7 electrodes × 8 EEG markers × 5 MMSE scores) and the level of significance set on $p < 0.05$.

Results

Demographic characteristics

Among 20 individuals enrolled to the study, the majority was female (70%). The mean age (±SD) was 69.85(±10.03). The mean MMSE overall score (±SD) was 15.15(±9.62) points that shows the majority of patients enrolled in the study had moderate-to-severe cognitive impairment. The pattern of approximately being half was repeated for each sub-scores (Table 1).

Correlations between MMSE scores and EEG markers recorded from frontal region electrodes

There was not any significant correlation between MMSE scores and each markers from Fp1, Fp2, F4, and F8. But, we found 9 significant correlations between MMSE scores and markers recorded from F7, F3, and Fz. Detailed results are presented in the following.

F7 recordings

The MMSE overall score was significantly and positively correlated with alpha relative power ratio ($p = 0.024$), that means with decrease in the MMSE overall score, the alpha relative power ratio decreases. The attention and calculation score was also positively correlated with alpha relative power ratio ($p = 0.007$). Any other significance has not been found for correlations between the MMSE scores and markers recorded from F7 (For details, see Table 2).

F3 recordings

The MMSE overall score was significantly and positively correlated with beta relative power ratio ($p = 0.006$). The orientation to time, orientation to place, and attention and calculation scores were also significantly and positively correlated with this feature with *p*-values equal to 0.011, 0.035, and 0.045, respectively. Any other significance has not been found for correlations between other MMSE scores and markers recorded from F3 (For details, see Table 3).

Fz recordings

The MMSE overall score was also significantly and positively correlated with beta relative power ratio ($p = 0.006$). The orientation to place, and attention and calculation scores were also significantly and positively

Table 1 Demographic characteristics: (A) Sex and education level, and (B) Mean age and MMSE scores with standard deviation (SD)

A	
N (%)	**20 (100)**
Sex	
Male	6 (30)
Female	14 (70)
Education level	
Illiterate	7 (35)
Literate	13 (65)

B		
	Mean	**± SD**
Age	69.85	10.03
MMSE overall score (30)	15.15	9.62
Orientation to time (5)	2.30	1.87
Orientation to place (5)	2.75	1.77
Attention and Calculation (17)	8.55	5.72
Recall (3)	1.40	1.04

Table 2 Correlations between MMSE scores and markers recorded from F7

F7	**Delta Median**	**Theta Median**	**Alpha Median**	**Theta/Alpha Power ratio**	**Delta Relative power**	**Theta Relative power**	**Alpha Relative power**	**Beta Relative power**
MMSE overall score	− 0.519 2.647	− 0.581 1.018	− 0.256 36.112	− 0.674 0.314	− 0.512 2.920	− 0.627 0.432	0.744 **0.024***	0.655 0.243
Orientation to time	− 0.509 3.062	− 0.604 0.666	− 0.453 6.317	− 0.543 3.379	− 0.371 15.030	− 0.640 0.332	0.523 2.511	0.704 0.0736
Orientation to place	− 0.381 13.699	− 0.474 4.882	− 0.216 50.315	− 0.538 4.026	− 0.328 22.123	− 0.630 0.410	0.586 0.932	0.582 1.000
Attention and calculation	− 0.505 3.261	− 0.541 1.930	− 0.188 59.788	− 0.677 0.295	− 0.550 1.670	− 0.559 1.446	0.781 **0.007***	0.592 0.836
Recall	− 0.474 4.876	− 0.510 3.026	− 0.243 42.312	− 0.629 0.836	− 0.495 3.700	− 0.510 3.044	0.660 0.215	0.551 1.645

Bold number means positive correlation. First line of each cell represents the Pearson correlation coefficient, and second line represents corrected *p*-value by multiplying by 280

Table 3 Correlations between MMSE scores and markers recorded from F3

F3	**Delta Median**	**Theta Median**	**Alpha Median**	**Theta/Alpha Power ratio**	**Delta Relative power**	**Theta Relative power**	**Alpha Relative power**	**Beta Relative power**
MMSE overall score	− 0.599 0.740	− 0.618 0.516	− 0.328 22.165	− 0.599 1.476	− 0.445 6.907	− 0.604 0.674	0.435 7.747	0.786 **0.006***
Orientation to time	− 0.642 0.315	− 0.667 0.185	− 0.528 2.342	− 0.415 19.192	− 0.330 21.822	− 0.531 2.231	0.214 51.040	0.766 **0.011***
Orientation to place	− 0.624 0.455	− 0.559 1.462	− 0.313 24.971	− 0.471 10.160	− 0.468 5.256	− 0.486 4.187	0.324 22.863	0.731 **0.035***
Attention and calculation	− 0.520 2.624	− 0.553 1.597	− 0.232 45.557	− 0.623 0.941	− 0.437 7.520	− 0.590 0.865	0.495 3.685	0.722 **0.045***
Recall	− 0.467 5.306	− 0.532 2.210	− 0.279 32.779	− 0.574 2.273	− 0.326 22.490	− 0.565 1.312	0.366 15.697	0.685 0.121

Bold number means positive correlation. First line of each cell represents the Pearson correlation coefficient, and second line represents corrected *p*-value by multiplying by 280

correlated with beta relative power ratio with *p*-values equal to 0.015, and 0.027, respectively. Any other significance has not been found for correlations between the MMSE scores and markers recorded from Fz (For details, see Table 4).

Fp1, Fp2, F4, and F8 recordings

Although we have not found any correlations for Fp1, Fp2, F4, and F8 electrodes, detailed results for these electrodes are presented in Table 5. It includes results of studies on alpha, and beta relative powers –i.e. the markers that showed correlations in studies on other electrodes.

Discussion

Our results indicate that there are correlations between frontal EEG markers and MMSE sub-scores of patients with AD. The results show that among 8 possible markers, the correlations are found only for alpha and beta relative powers. These correlations are consistent with results of Garn et al. study that examined the associations between relative powers and MMSE scores. They found that increasing resting state alpha, delta, and beta relative powers are significantly explainable by increasing MMSE scores [15]. In this study, we found that alpha and beta relative powers are positively correlated with MMSE scores that replicates a part of what Garn et al. found. Cecchetti et al. conducted a study using functional MRI data, laboratory results of cerebrospinal fluid, to evaluate resting state EEG biomarker in diagnosis of AD. Although, they found that theta frequency is earliest and the most sensitive EEG biomarker of AD, they also suggested that alpha band is also a potential biomarker for neurodegeneration [33].

Our results show no strong correlations between resting-state EEG markers and MMSE scores in Fp1 and Fp2, as Choi et al. found that there is a moderate correlation [16]. While Doan et al. based on correlations they have found for prefrontal recordings (i.e., Fp1, and Fp2),

Table 4 Correlations between MMSE scores and markers recorded from Fz

Fz	Delta Median	Theta Median	Alpha Median	Theta/Alpha power ratio	Delta Relative power	Theta Relative power	Alpha Relative power	Beta Relative power
MMSE overall score	− 0.439 7.388	− 0.568 1.260	− 0.199 55.905	− 0.599 1.460	− 0.357 17.048	− 0.614 0.561	0.313 25.099	0.785 **0.006***
Orientation to time	− 0.426 8.594	− 0.582 1.001	− 0.372 14.883	− 0.393 24.218	− 0.253 39.417	− 0.508 3.097	0.081 102.893	0.759 **0.015***
Orientation to place	− 0.411 10.030	− 0.464 5.504	− 0.153 72.828	− 0.470 10.176	− 0.381 13.684	− 0.452 6.345	0.237 43.999	0.673 0.159
Attention and Calculation	− 0.411 10.098	− 0.529 2.294	− 0.132 80.928	− 0.632 0.778	− 0.358 16.934	− 0.619 0.507	0.384 13.118	0.739 **0.027***
Recall	− 0.344 19.295	− 0.513 2.887	− 0.191 58.924	− 0.567 2.544	− 0.238 43.703	− 0.596 0.778	0.234 44.818	0.699 0.085

Bold number means positive correlation. First line of each cell represents the Pearson correlation coefficient, and second line represents corrected *p*-value by multiplying by 280

Table 5 Results of study on correlations between MMSE scores and alpha, and beta relative powers recorded from Fp1, Fp2, F4, and F8 electrodes

Electrode	Fp1		Fp2		F4		F8	
Marker	Alpha Relative power	Beta Relative power	Alpha Relative power	Beta Relative power	Alpha Relative power	Beta Relative power	Alpha Relative power	Beta Relative power
MMSE overall score	0.412 9.947	0.475 4.812	0.420 9.083	0.400 11.262	0.446 6.788	0.477 4.675	0.699 0.084	0.457 6.018
Orientation to time	0.214 51.239	0.570 1.219	0.224 47.974	0.499 3.500	0.191 58.664	0.595 0.797	0.528 2.347	0.547 1.765
Orientation to place	0.340 20.023	0.445 6.938	0.340 19.981	0.365 15.912	0.357 17.086	0.454 6.211	0.586 0.925	0.432 7.961
Attention and Calculation	0.460 5.762	0.402 11.067	0.470 5.127	0.342 19.655	0.504 3.286	0.409 10.218	0.711 0.061	0.392 12.259
Recall	0.323 23.024	0.407 10.453	0.330 21.683	0.309 25.921	0.411 10.083	0.326 22.414	0.615 0.543	0.356 17.288

First line of each cell represents the Pearson correlation coefficient, and second line represents corrected *p*-value by multiplying by 280. No significant correlation has been found

concluded that prefrontal EEG biomarkers can be predicting dementia [17], we suggest that it would be helpful to consider correlations between MMSE scores and EEG markers recorded from F3, F7, and Fz (See Tables 2, 3, 4). It seems that if we want to develop predicting models for AD, using data recorded from other frontal electrodes, especially what we have introduced should be considered.

The main benefit that can be gotten from our results is to use them to develop models for diagnosis of AD. These models simply get data from electrode recordings and give a prediction of the severity of the disease. Many other outputs can be conceived with various purposes. For example, we can change the output to the level of response to a specific medication, or change it to the type of dementia, etc. A good example of this modeling is what Choi et al. introduced for predictive model to early diagnosis of dementia, using EEG signals [16]. However, our results are not the same with what Choi et al. introduced. It may be used for assessments of cognitive abilities in more severe cases, and for modeling the prognosis of disease.

In this study, we generally examined correlations in AD patients. We propose three other areas that are very close to the subject of this study. First, it is conceivable to design studies on correlations of MMSE scores and EEG markers to compare AD with non-AD patients. These studies should be performed to find differences between types of dementia. Those studies would help to develop precise models to differentiate between AD from other types of dementia. Second, another subject that can be pursued by further studies is evaluating effects of sociodemographic characteristics on the correlations between MMSE scores and EEG markers. Finally, to study relationships of the correlations with prognoses of patients, we propose designing cohort studies, exactly with the same method. The recorded data in cohort study would provide evidence for predicting models for patients' prognoses.

Limitations

Our study had at least two limitations: (1) limited number of eligible patients enrolled in the study, (2) absence of control groups—e.g., healthy group or non-AD patients with other types of dementia. Because this study was not supported by any grants, it was difficult for us to address these limitations.

Conclusions

Following recent studies to develop diagnostic tools for AD based on qEEG, we suggest that it can be effective if it is indicated that EEG biomarkers recorded from which electrodes show strongest correlations with AD. Reliable strong correlations guide us to develop predicting models more confident. Therefore, we hope that further studies on this topic indicate this issue.

Abbreviations

AD: Alzheimer's Disease; MMSE: Mini Mental State Examination; EEG: Electroencephalography; SD: Standard deviation.

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Authors' contributions

All authors have contributed in idea generation, data acquisition, data analysis, writing the manuscript, and editing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data are storage by the Asab Pajoohan Farda Research Company.

Declarations

Ethical approval and consent to participate

Ethical approval was taken from Research Ethical Committee of Institute for Cognitive and Brain Sciences, Shahid Beheshti University. Informed consents for entering to the study were taken by caregivers of patients.

Consent for publication

All the authors have consented for the publication.

Competing interests

There is no competing interests in this research.

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