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Original Article / Özgün Araştırma

Resting-state EEG Findings in Differentiating Alzheimer's Disease From Amnestic Mild Cognitive Impairment and Healthy Elderly Controls

İstirahat EEG Aktivitesi Alzheimer Hastalığını Amnestik Hafif Kognitif Bozukluk ve Sağlıklı Bireylerden Ayırt Edebilir

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Abstract

Objective: We aimed at investigating alterations in Resting-State electroencephalography (rsEEG) patterns of individuals with amnestic mild cognitive impairment (aMCI), and Alzheimer's disease (AD).

Materials and Methods: Twenty healthy controls (HC) with 20 aMCI, and 20 AD patients were included in the study. EEG data was recorded for 4 minutes of eyes-closed condition according to the International 10-20 system. EEG rhythms of interest were delta (0.5-3.9 Hz), theta (4-7.8 Hz), alpha 1 (8-10.4 Hz), alpha 2 (10.5-13 Hz), and beta (13-30 Hz). The discriminatory power of rsEEG between groups was evaluated using the receiver operating characteristic analysis. Correlations among cognitive scores and power values of rsEEG were analyzed using Pearson correlation analysis.

Results: We observed effects on delta [$F_{(2,57)}$: 8.353; p=0.001], theta [$F_{(2,57)}$: 5.038; p=0.010], alpha 1 [$F_{(2,57)}$: 3.837; p=0.027], and alpha 2 [$F_{(2,57)}$: 4.209; p=0.020] power between groups. Moreover, interaction effects for anterior-posterior electrode location x group on delta [$F_{(6,171)}$: 2.621; p=0.038], and theta [$F_{(6,171)}$: 3.537; p=0.020] power were also detected. AD group demonstrated decreased delta power in frontal, central and parietal locations (for all; p<0.040) compared to HC and aMCI groups. In addition, the AD group also had decreased alpha and alpha1 power in comparison with HC (for all; p<0.026). Furthermore, we recorded a sensitivity of 80.0% and a specificity of 80.0% of delta power when using the cut-off score of >1.71 to identify AD from aMCI at central electrodes, and >1.73 to identify AD from HC at parietal electrodes. Moderate correlations were also detected among cognitive scores and rsEEG rhythms.

Conclusion: This study revealed the importance of delta and theta activity in rsEEG both as an electrophysiological indicator of cognitive status in AD and as a discriminatory tool for detecting aMCI.

Keywords: Alzheimer's disease, mild cognitive impairment, resting-state EEG, delta, theta

Öz

Amaç: Bu çalışmada, amnestik hafif kognitif bozukluk (aHKB) ve Alzheimer hastalığı (AH) olan bireylerin istirahat elektroensefalografi (EEG) aktivitelerinin incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Yirmi AH ve 20 aHKB tanılı bireyler ile demografik açıdan eşleştirilmiş 20 sağlıklı gönüllü çalışmaya dahil edilmiştir. Dört dakikalık, gözler kapalı durumda EEG kaydı uluslararası 10-20 sistemine göre alınmıştır. İki saniyelik dilimlere ayrılan EEG verisine hızlı fourier dönüşümü uygulanmıştır. Grupların delta (0,5-3,9 Hz), teta (4-7,8 Hz), alfa 1 (8-10,4 Hz), alfa 2 (10,5-13 Hz) ve beta (13-30 Hz) olmak üzere tüm frekans bantlarındaki güç değerleri ölçülmüştür. EEG analizleri tekrarlanan ölçümlerle ANOVA ile yapılmıştır. İstatistiksel açıdan anlamlı bulunan frekans bantlarındaki güç değerlerinin gruplardaki ayırt ediciliğinin belirlenmesi ROC eğrisi (Alıcı İşletim Karakteristikleri, Receiving Operating Characteristics) ile analiz edilmiştir. Kognitif skorlar ve her bir frekanstaki güç değerleri arasındaki ilişkiler Pearson korelasyon analizi ile değerlendirilmiştir.

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Bulgular: Delta [$F_{(2,57)}$: 8,353; p=0,001], teta [$F_{(2,57)}$: 5,038; p=0,010], alfa [$F_{(2,57)}$: 3,837; p=0,027] ve alfa 1 [$F_{(2,57)}$: 4,209; p=0,020] gücü ölçümlerinde ana grup etkisi bulunmuştur. Ayrıca, anterior-posterior elektrot yerleşimi x grup etkileşim etkileri delta [$F_{(6,171)}$: 2,621; p=0,038] ve teta [$F_{(6,171)}$: 3,537; p=0,020] gücünde saptanmıştır. AH olguları yüksek delta ve teta gücü ile sağlıklı gönüllüler ve aHKB grubundan istatistiksel olarak anlamlı düzeyde farklılaşmaktadır (tümü için; p<0,040). Ayrıca, sağlıklı gönüllülere kıyasla, AH grubu düşük alfa ve alfa 1 gücü göstermiştir (tümü için; p<0,026). ROC eğrisi analizlerinde, delta gücünün AH'yi aHKB'den >1,71 kesme puanı ile santral elektrotlarda, sağlıklı kontrollerden >1,73 kesme puanı ile parietal elektrotlarda %80 duyarlılık ve %80 özgüllük ile ayırt edebildiği görülmüştür. Ayrıca grupların kognitif skorları ve farklı frekans bantlarındaki güç değerleri arasında orta düzeyde korelasyonlar saptanmıştır.

Sonuç: Bu çalışma, istirahat EEG'sinde delta ve teta aktivitesinin hem AH'de kognitif durumun bir belirteci olarak hem de aHKB'den ayırt edilmesindeki önemine işaret etmektedir.

Anahtar Kelimeler: Alzheimer hastalığı, hafif kognitif bozukluk, istirahat EEG'si, delta, teta

Introduction

Alzheimer's disease (AD) is known as a common cause of dementia and constitutes approximately 70% of all dementias (1). It is characterized by impairment in episodic memory domain with the atrophy of the entorhinal cortex, hippocampus, and external temporal associative regions (2). Diagnosing AD can be problematic in the early stages as it usually starts with memory problems that can mimic the normal aging process. From this observation, recent studies have focused on the intermediate stage between normal aging and the diagnosis of clinically probable AD. This zone has been defined as mild cognitive impairment (MCI), dementia prodrome, incipient dementia, and isolated memory impairment among others (3). Amnestic MCI (aMCI) is characterized by episodic memory impairments detectable by neuropsychological tests as in AD. Meanwhile, daily life activities remain intact. Clinical examination has been considered as the gold standard in the diagnosis of MCI and AD (4,5). However, retrospective evaluation of medical records and neuropsychological assessment require lengthy sessions with experienced clinicians and neuropsychologists, making the diagnosis of MCI and AD time-consuming and irreproducible. Due to these drawbacks, alternative cost effective methods are needed for easier and more convenient diagnosis.

Electroencephalography (EEG) is a non-invasive, cost effective method with high temporal resolution commonly used in clinical research. Several electrophysiological methods such as event-related potentials and oscillations are used to evaluate the brain activity during a cognitive task. However, due to cognitive impairments, it may be problematic to prefer such methods when investigating individuals with AD. Instead, resting-state EEG (rsEEG) may present neural responses associated with sensory and cognitive processes using different mathematical techniques in individuals with AD. The most prominent finding regarding AD in rsEEG is the increase in low-frequency power [(delta (0.5-4 Hz), theta (4-8 Hz)] in the posterior regions and decrease in high-frequency power [alpha (8-13 Hz), beta (15-30 Hz)] (1). Moreover, decrease in alpha power in the temporal, parietal and occipital areas is associated with hippocampal atrophy (6). In another study by Babiloni et al. (7), increased frontal delta and occipital theta power were observed when comparing individuals with MCI and health controls. Furthermore, associations between frontal delta power and the scores evaluating general cognitive status have been reported in individuals with MCI.

Clinical evaluation through neuropsychological measures is recognized as the gold standard in detecting MCI and AD. Non-etheless, some limitations may arise due to retrospective evaluation of medical records, inadequate normative data, and lengthy administration sessions (8). Recently, there is a great focus on EEG parameters as a non-invasive and cost effective method in differentiating healthy control (HC) from individuals with MCI and those with AD. In some cases, significant differences were found among groups; however, different group means does not always present a good diagnostic classification among them (9). In clinical settings, criterion validity of a screening tool is crucial. EEG markers were suggested as a strong tool for discriminating patients with dementia from healthy individuals. High discriminative power was also reported when classifying different types of dementia (10,11,12,13). However, only few studies have investigated the discriminative power of the rsEEG markers to differentiate between HC, individuals with MCI and AD. Snaedal et al. (10) reported high discriminative power for healthy individuals versus AD patients, healthy individuals versus patients with MCI and patients with MCI versus those with AD. However, a more recent study stated that the differences in the MCI group was small and localized compared to the AD group (14). Another study reported only increased pre-alpha powers in individuals with MCI compared to HC in a wide range of rsEEG measures (13).

In the present study, we aimed at investigating the criterion validity of the EEG spectral power between HC, patients with MCI and those with AD using the receiver operating characteristic (ROC) curve analysis. We also sought to determine the cut-off values with optimal sensitivity and specificity for screening. To achieve this aim, we first investigated the rsEEG power differences among groups in all frequency bands to identify the possible candidates for rsEEG markers. Our principal hypotheses for this study were as follows: Firstly, individuals with AD would have increased delta and theta power compared to those with aMCI and HC, while decreased power was detected in alpha and beta bands; secondly, the aMCI group would have decreased power in delta and theta bands compared to the other groups. The frequency bands that showed differences among groups were further analyzed using the ROC curve analysis. Finally, the correlations between power values and z-scores of cognitive domains of the groups were evaluated.

Materials and Methods

Participants

Twenty HC, twenty individuals with aMCI, and twenty individuals with AD participated in our study. Individuals with AD were recruited from the outpatient units in accordance with the core clinical criteria for probable AD dementia of the National Institute on Aging/Alzheimer's Association (NIA-AA) (5). The

clinical diagnosis was determined by a consensus of neurologists and neuropsychologists, considering individuals had; 1) insidious onset mild-to-moderate AD based on clinical dementia rating scale [(CDR): 1&2], 2) impairments in two or more cognitive areas, 3) history of progressive worsening of cognitive functions through neuropsychological tests, 4) mini-mental state examination (MMSE) score <24. Furthermore, 12 AD patients were on anticholinesterase drugs (donepezil; 5-10 mg per day, and rivastigmine; 6-9.5 mg per day). Moreover, four individuals with AD were treated with memantine (20 mg per day) in addition to anticholinesterase agents, while four AD patients were only on memantine. Individuals with aMCI were identified based on the core clinical criteria of the NIA-AA including; preserved daily life activities, concerns related to a change in cognition acquired from the patient and/or from an informant who knows the patient well, and an impaired performance shown by neuropsychological tests on memory (≥1.5 SD of the normative data) (4).

The exclusion criteria for all groups were as follows: having depressive symptoms [Yesavage geriatric depression scale, (GDS) score >14]; having other neurologic and/or psychiatric disorders, history of stroke, head injury, alcohol and/or drug abuse; presence of brain tumor and/or vascular lesions which may affect cognitive functions, and; having less than 80 artifact-free EEG epochs. HC who do not have any cognitive impairment and/or neurological abnormality (MMSE score ≥28; CDR: 0) were also included in the study. Twenty individuals with aMCI, twenty with AD, and twenty HC matched in terms of age, gender and education were consecutively recruited and included. Ethical approval for this study was obtained by the Dokuz Eylul University Non-interventional Research Ethics Committee (decision no: 2018/05-09, date: 15.02.2018). Written informed consent was collected from all participants or their caregivers.

There were no significant differences in age, education, gender, handedness, GDS score, and epoch number. On the other hand, individuals with AD had significantly lower MMSE scores than the other groups as expected (p<0.001). A summary of demographic and clinical features of study participants is displayed in Table 1.

Neuropsychological Measures

Cognitive performances of all participants were assessed by neuropsychologists. Neuropsychological tests covering cognitive domains such as attention, episodic memory, executive functions, and language were performed. Episodic memory was evaluated using Oktem Verbal Memory Processes Test (OVMPT) which also covers immediate recall, total learning and delayed recall (15). Wechsler Memory scale-revised (WMS-R) Visual Reproduction Subtest was used to evaluate visual memory (16). WMS-R Digit Span test, Stroop test (17), and phonemic fluency test were performed to assess attention and executive functions while language skills were evaluated with the 15-item version of Boston naming test (18), and semantic fluency test. In order to form composite scores, raw neuropsychological test scores were transformed to z-scores. Subsequently, the z-scores were combined to generate composite ones for each cognitive domain (language, attention/executive functions, and memory). Memory domain included the OVMPT, total learning, immediate recall, and delayed recall scores. The domain of attention/executive functions included the digit span, Stroop test interference score, and phonemic fluency scores. The language domain included Boston naming, and semantic fluency scores. Individuals with AD demonstrated decreased scores on episodic memory (p<0.002), language (p<0.016), and attention/executive function (p<0.008) domains than the other groups as expected.

Electrophysiological Recording and Analysis Steps

EEG recordings were done using 30 Ag-AgCI electrodes placed on an elastic cap (EasyCap; Brain Products GmbH; Gliching, Germany) in a sound-attenuated and electrically shielded room in accordance with the international 10/20 montage system. Linked earlobe electrodes (A1+A2) were used as reference electrodes. Horizontal and vertical electrooculograms were recorded from

Table 1. Demographic, clinical and cognitive features of participants

	HC (n=20)	aMCI (n=20)	AD (n=20)	p	HC & aMCI	HC & AD	aMCI & AD
Age	71.95±3.20	72.05±4.49	74.15±4.77	0.185[a]	-	-	-
Education	8.95±5.32	9.60±4.66	9.50±4.92	0.906[a]	-	-	-
Gender (F/M)	12/8	9/11	11/9	0.626[b]	-	-	-
Handedness (R/L/both)	19/1	19/1	19/0/1	0.558[b]	-	-	-
MMSE	28.90±1.07	26.45±2.26	19.00±6.39	**<0.001**[a]	0.156	**<0.001**	**<0.001**
GDS	5.20±4.58	8.10±4.87	6.00±4.43	0.136[a]	-	-	-
Epoch number	95.10±11.88	97.00±7.92	96.85±11.40	0.819[a]	-	-	-
Memory	0.00±0.80	-5.02±1.98	-8.46±1.30	**<0.001**[a]	**<0.001**	**<0.001**	**<0.001**
Attention/executive functions	0.00±0.57	-0.54±0.89	-1.32±0.78	**<0.001**[a]	0.091	**<0.001**	**0.007**
Language	0.00±0.58	-0.90±1.52	-2.35±2.10	**<0.001**[a]	0.233	**<0.001**	**0.015**

Data are reported as mean ± standard deviation. Findings of the ANOVA model and pairwise comparisons based on Bonferroni correction are equally presented. [a]Analysis of variance test, [b]Chi-square test, HC: Healthy controls, aMCI: Amnestic mild cognitive impairment, AD: Alzheimer's disease, F: Female, M: Male, R: Right, L: Left, MMSE: Mini-mental state examination test, GDS: Yesavage geriatric depression scale

the outer canthus of the right eye and the supraorbital region, respectively. For all electrodes, impedances were kept below 10 kΩ. The BrainAmp 32-channel DC system amplified the signals with a high-frequency cut-off of 70 Hz, and a sampling rate of 500 Hz.

Only 4 minutes of eyes-closed condition was included in the analyses. Brain Vision Analyzer 2.1 (Brain Products GmbH; Gilching, Germany) was used to analyze data. Continuous EEG data were filtered between 0.5-30.0 Hz, and a 50 Hz-Notch filter was applied. Filtered data were segmented into 2000 ms epochs. EEG epochs with artifacts (muscle activity, sweating, and eye movements) were automatically rejected, and each epoch was manually checked. Due to the insufficient number of epochs, three HC, two individuals with aMCI, and three with AD were excluded. The remaining 20 individuals with aMCI, 20 with AD, and 20 HC were included in further analyses. Fast fourier transform (FFT) was applied to obtain power values in each frequency band, and grand average waveforms for groups were computed. Power values in delta (0.5-3.9 Hz), theta (4.0-7.9 Hz), alpha (8.0-13.0 Hz), alpha 1 (8.0-10.4 Hz), alpha 2 (10.5-13.0 Hz), beta (13.0-30.0 Hz) frequency bands were automatically measured at F_3, F_z, F_4, C_3, C_z, C_4, P_3, P_z, P_4, O_1, O_z, and O_2 electrode locations. For each frequency band, the averages of the power values at the frontal (F_3, F_z, F_4), central (C_3, C_z, C_4), parietal (P_3, P_z, P_4) and occipital (O_1, O_z, O_2) electrode locations were included in the analyses.

Statistical Analysis

Statistical analysis was performed using the SPSS version 24.0 for Windows (IBM; Armonk, NY, USA). Neuropsychological measures, demographic, and clinical features of the groups were analyzed using One-Way ANOVA. Separate repeated measures ANOVAs were performed for delta (0.5-3.9 Hz), theta (4.0-7.9 Hz), alpha (8.0-13.0 Hz), alpha 1 (8.0-10.4 Hz), alpha 2 (10.5-13.0 Hz), and beta (13-30 Hz) frequency bands. The ANOVA design consisted of anterior-posterior (AP) electrode location (AP: frontal, central, parietal, occipital) for a within-subject factor, and group (3 levels: HC, aMCI, AD) for a between-subject factor. Post-hoc analyses were operated through Bonferroni correction. Considering only significant power values for frequency bands, the ROC curves with area under the curve (AUC) (95% confidence interval) were evaluated in order to define the cut-off value for distinguishing groups. Correlations among rsEEG power values of frequency bands and scores of cognitive domains were assessed using Pearson correlation analysis. The value of statistical significance was corrected for multiple comparisons using Bonferroni correction. Correlations were first assessed on the whole sample, and then separately within HC, AD, and aMCI groups.

Results

The means of the power values in delta (0.5-3.9 Hz), theta (4.0-7.9 Hz), alpha (8.0-13.0 Hz), alpha 1 (8.0-10.4 Hz), alpha 2 (10.5-13.0 Hz), beta (13.0-30.0 Hz) frequency bands among groups are presented in Figure 1.

Resting-state Delta and Theta Power

Repeated ANOVA measures revealed effects on delta [$F_{(2.57)}$: 8.353; p=0.001], and theta [$F_{(2.57)}$: 5.038; p=0.010] power, indicating individuals with AD had increased delta (p<0.004) and theta (p<0.028) power compared to the other groups (Table 2).

Moreover, interaction effects of AP x group on delta [$F_{(6.171)}$: 2.621; p=0.038], and theta [$F_{(6.171)}$: 3.537; p=0.020] power were observed, demonstrating that AD had increased delta and theta power in frontal, central, and parietal electrode areas (for all; p<0.040) compared to the other groups. Furthermore, there is a main effect for AP in delta power [$F_{(3.171)}$: 25.188; p<0.001], revealing that delta power were higher in frontal, central, and parietal areas compared to occipital areas (p<0.001). There is also a main effect for AP in theta power [$F_{(3.171)}$: 9.286; p=0.001], demonstrating that theta power measured at frontal locations was significantly higher than those at central, and occipital electrode locations (p<0.005). Increased theta power was also measured at central, and parietal areas in comparison to occipital locations (p<0.042). The bar plots of the average delta and theta powers recorded from frontal, central, parietal, and occipital electrode areas among groups are presented in Figure 2.

Resting-state Alpha (8-13 Hz) and Beta Power (13-30 Hz)

There was a main group effect on alpha [$F_{(2.57)}$: 3.837; p=0.027] power, demonstrating individuals with AD had significantly decreased alpha powers compared to HC (p=0.025). Moreover,

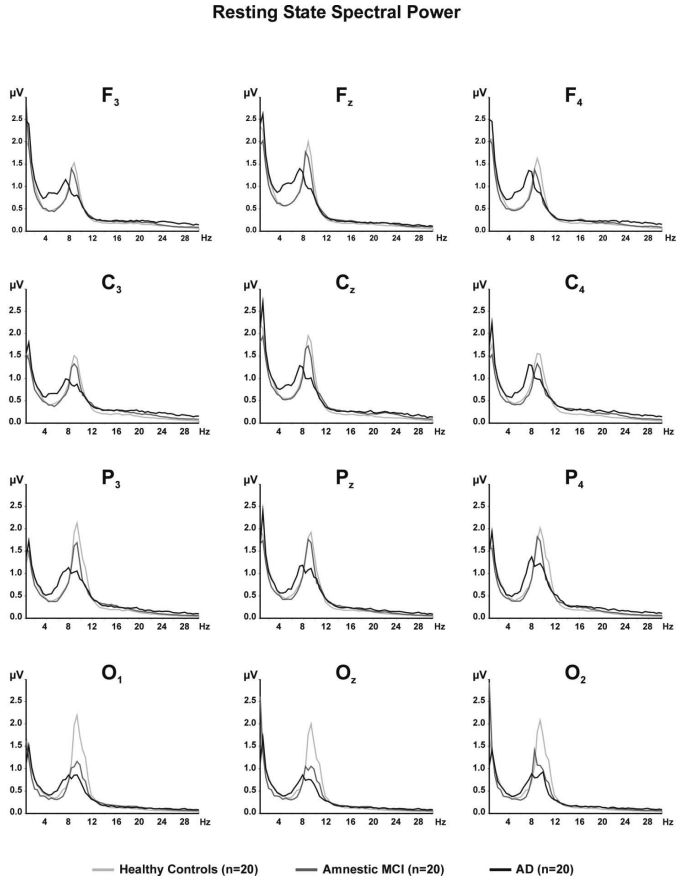

Figure 1. Overall averages of the rsEEG power values over electrode locations

rsEEG: Resting-state electroencephalography, MCI: Mild cognitive impairment, AD: Alzheimer's disease

a main effect for AP in alpha power was also detected [$F_{(3.171)}$: 3.387; p=0.040], showing that alpha power measured at parietal electrode locations was significantly higher than those at occipital locations (p=0.013).

Secondly, repeated ANOVA measures also revealed an effect on alpha 1 power [$F_{(2.57)}$: 4.209; p=0.020], revealing that decreased alpha 1 power was found in the AD group compared to HC (p=0.016). Moreover, a main effect of AP for alpha 1 power was also detected [$F_{(3.171)}$: 5.195; p=0.007], indicating that alpha 1 power values at parietal electrode locations were significantly higher than those at occipital locations (p=0.001). However, there was no effect on alpha 2 power values [$F_{(2.57)}$: 0.140; p=0.869].

Moreover, there was no effect on beta power values as well [$F_{(2.57)}$: 0.972; p=0.385]. The bar plots of the average alpha, alpha 1, alpha 2 and beta power values recorded from frontal, central, parietal, and occipital electrode areas among groups are presented in Figure 3.

ROC Curve Analyses for Delta and Theta Power

The ROC curve analyses for distinguishing the AD group from the aMCI group, and the AD group from HC revealed high sensitivity and specificity values for delta and theta power. The results derived from the ROC curve analysis are shown in Table 3. The ROC curves of delta power to distinguish individuals with AD from HC and from aMCI are displayed in Figure 4.

Correlations of Cognitive Scores and Power Values

Correlations were first analyzed on the whole sample, and then separately within the HC, AD, and aMCI groups. Table 4 presents the significant correlations after the Bonferroni correction.

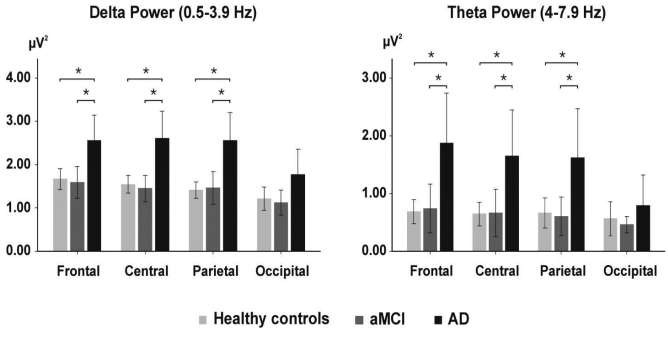

Figure 2. The averages of delta and theta power values over electrode locations
**Indicates a significant difference between electrode placements (p<0.05).*
aMCI: Amnestic mild cognitive impairment, AD: Alzheimer's disease

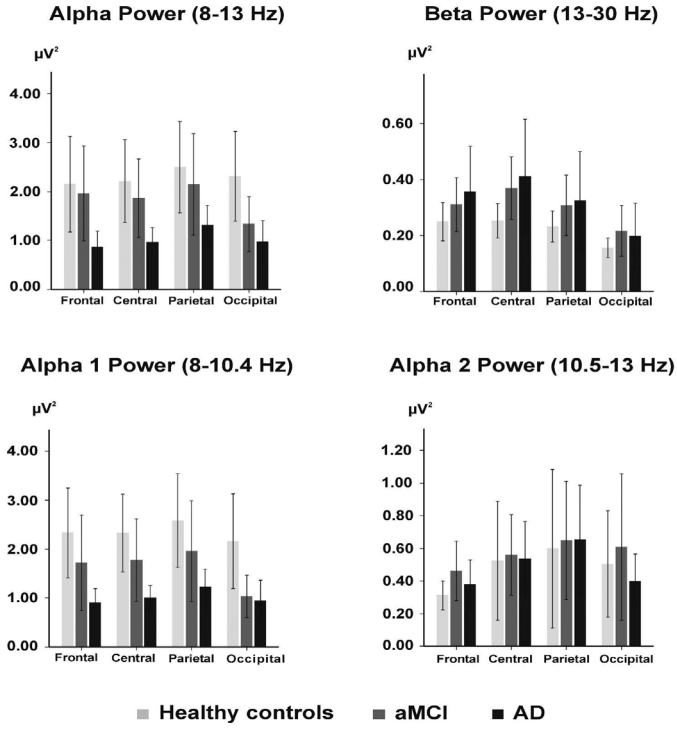

Figure 3. The averages of alpha, alpha 1, alpha 2 and beta power values over electrode locations
aMCI: Amnestic mild cognitive impairment, AD: Alzheimer's disease

Table 2. Averages of delta (0.5-3.9 Hz) and theta (4-7.9 Hz) power among groups

	HC (n=20)	aMCI (n=20)	AD (n=20)	Further analyses		
				HC & aMCI	HC & AD	aMCI & AD
Delta						
Frontal	1.67±0.52	1.59±0.79	2.55±1.25	**1.000**	**0.009**	**0.004**
Central	1.54±0.43	1.45±0.65	2.61±1.34	**1.000**	**0.001**	**<0.001**
Parietal	1.41±0.40	1.46±0.80	2.56±1.38	**1.000**	**0.001**	**0.002**
Occipital	1.21±0.57	1.12±0.61	1.77±1.27	1.000	0.151	0.072
Theta						
Frontal	0.69±0.45	0.74±0.90	1.87±1.85	**1.000**	**0.009**	**0.014**
Central	0.65±0.44	0.66±0.88	1.65±1.71	**1.000**	**0.022**	**0.025**
Parietal	0.66±0.56	0.61±0.71	1.62±1.82	**1.000**	**0.039**	**0.026**
Occipital	0.56±0.63	0.46±0.30	0.79±1.13	1.000	1.000	0.534

Data are reported as mean ± standard deviation in μV^2. HC: Healthy controls, aMCI: Amnestic mild cognitive impairment, AD: Alzheimer's disease

Discussion

The purpose of this study was to determine the criterion validity of the rsEEG spectral power between HC, patients with MCI and AD. Individuals with AD had lower alpha power compared to HC, and increased delta and theta power compared to HC and patients with aMCI. Delta and theta power were found as the strongest indicators in distinguishing AD from aMCI and HC.

Recent studies have focused on non-invasive, fast, and low-cost diagnostic procedures which can be easily applied in clinical practice. rsEEG is a cost effective and a non-invasive tool widely used in clinical settings to investigate brain activity. Moreover, EEG power analyses provide information about cortical neural synchronization (6). ROC curve analysis is used to discriminate between two groups by defining sensitivity and specificity for the entire range of possible cut-off points. An AUC of 0.7-0.8 was considered as acceptable and of 0.8-0.9 as an excellent discrimination (19). In this study, delta and theta power were found to be sensitive for differentiating individuals with AD from those with aMCI and HC.

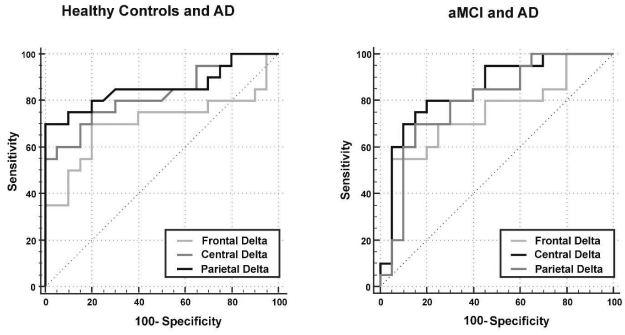

Figure 4. The ROC curves for delta power
ROC: Receiver operating characteristic, aMCI: Amnestic mild cognitive impairment, AD: Alzheimer's disease

Our findings revealed that the central and parietal delta power had excellent discriminative power between individuals with AD and HC. Moreover, central delta power showed an excellent discrimination between individuals with AD and those with aMCI. A previous study used a different method (other than FFT) and showed that aMCI differ from AD with an accuracy of 92.33% (20). Furthermore, alpha and delta power ratio in the posterior cortical region detected AD from HC with a 73% sensitivity and 78% specificity in an rsEEG study using FFT analysis (21). Lizio et al. (22) also reported that AD patients were separated from HC using the delta-alpha power ratio over the parieto-occipital region with a sensitivity of 77.2%. Thus, rsEEG measures can be used to distinguish individuals with AD from HC and different methodologies may increase the discrimination accuracy.

Many studies reported differences between individuals with AD and HC in quantitative EEG studies using FFT analysis. Increase in theta power and a decrease in beta power were the earliest changes in AD, followed by a decrease in alpha power. In addition, higher delta power may also be detected in the later stages of the disease (23). In line with previous literature, individuals with AD showed increased delta and theta power compared to those with aMCI and HC while decreased alpha power was detected in those with AD.

Table 3. Sensitivity and specificity of delta (0.5-3.9 Hz) and theta (4-7.9 Hz) power

	Cut-off value (μV)	Sensitivity	Specificity	AUC (CI 95%)	p value
Delta (0.5-3.9 Hz)					
HC & AD					
Frontal	>1.91	70.00	80.00	0.705 (0.540-0.838)	**0.0227**
Central	>1.71	80.00	70.00	0.826 (0.674-0.927)	**<0.0001**
Parietal	>1.73	80.00	80.00	0.859 (0.712-0.948)	**<0.0001**
aMCI & AD					
Frontal	>1.80	70.00	75.00	0.742 (0.580-0.867)	**0.0030**
Central	>1.71	80.00	80.00	0.848 (0.699-0.941)	**<0.0001**
Parietal	>1.69	80.00	70.00	0.795 (0.638-0.906)	**0.0001**
Theta (4-7.9 Hz)					
HC & AD					
Frontal	>0.72	75.00	65.00	0.750 (0.588-0.873)	**0.0025**
Central	>0.41	80.00	40.00	0.722 (0.558-0.852)	**0.0102**
Parietal	>0.37	80.00	45.00	0.645 (0.478-0.790)	0.1160
aMCI & AD					
Frontal	>0.75	75.00	80.00	0.760 (0.599-0.881)	**0.0024**
Central	>0.55	75.00	75.00	0.749 (0.587-0.872)	**0.0033**
Parietal	>0.47	70.00	60.00	0.693 (0.527-0.828)	**0.0274**

HC: Healthy controls, aMCI: Amnestic mild cognitive impairment, AD: Alzheimer's disease, CI: Confidence interval, AUC: Area under the curve

Table 4. Correlations of cognitive scores and power values of frequency bands

	MMSE	Memory	Attention/executive functions	Language
Whole sample				
Delta-frontal	r=-0.536, p<0.001	-	r=-0.416, p=0.001	-
Delta-central	r=-0.655, p<0.001	r=-0.372, p=0.003	r=-0.406, p=0.001	-
Delta-parietal	r=-0.669, p<0.001	r=-0.395, p=0.002	r=-0.389, p=0.002	r=-0.404, p=0.002
Delta-occipital	r=-0.526, p<0.001	-	-	-
Theta-frontal	-	-	r=-0.389, p=0.002	r=-0.483, p<0.001
Theta-central	r=-0.376, p=0.003	-	r=-0.401, p=0.002	r=-0.502, p<0.001
Theta-parietal	r=-0.396, p=0.002	-	-	r=-0.416, p=0.001
aMCI				
Delta-parietal	-	-	-	r=-0.663, p=0.003
Delta-occipital	-	-	-	r=-0.664, p=0.003
Theta-frontal	-	-	-	r=-0.747, p<0.001
Theta-central	-	-	-	r=-0.732, p=0.001
Theta-parietal	-	-	-	r=-0.710, p=0.001
Alpha 2-frontal	-	-	-	r=-0.676, p=0.002
AD	-	-	-	-
Delta-parietal	r=-0.651, p=0.003	-	-	-
Delta-occipital	r=-0.650, p=0.003	-	-	-

MMSE: Mini-mental state examination, aMCI: Amnestic mild cognitive impairment, AD: Alzheimer's disease

The distribution of neurofibrillary elements in AD is compatible with the projection of anatomic-functional cycles in the brain. Degeneration of corticopyramidal neurons leads to disconnection and interruption of cortico-cortical association pathways (24). Disease progression with cholinergic deterioration and loss of cholinergic innervation in the neocortex are the major pathophysiological processes underlying EEG abnormalities (hallmarked by slowing of the rhythms) in AD (25).

Alpha power is associated with thalamo-cortical and cortico-cortical interactions that influence the transmission of sensorimotor information between cortical and subcortical pathways, and recall of semantic information from cortical stores (26). High alpha power (10-13 Hz) is involved in the processing of task-specific sensorimotor and semantic information, while low alpha power (8-10 Hz) is associated with the mental preparation process. Moreover, Babiloni et al. (27) reported that alpha power density in the posterior region is related to physiological aging and global cognitive level. However, beta oscillations during rsEEG are less common to elicit. Beta oscillations may occur during cognitive tasks related to executive and visual functions, in situations requiring maximum attention due to anxiety or under the influence of medication (28). In this study, there were no differences in alpha and beta power between individuals with aMCI and AD. According to Babiloni et al. (29), rsEEG power could differentiate individuals with AD from those with aMCI only with high risk of progression to AD. In other words, aMCI group with increased theta and delta power, and low alpha power were found to be indicative for the progression to dementia in a 1-year follow-up. Furthermore, impairment in cognitive function remained stable in patients with aMCI with high posterior alpha power. In this context, our aMCI group did not consist of individuals at high risk of progression to AD due to lack of information about CSF markers. This could also explain why no differences were detected by alpha/beta power among aMCI and AD groups.

Several studies reported a decrease in the posterior alpha rhythm in patients with aMCI, (7,24,27,30) whereas increased theta power (23), and decreased beta power (31) were detected in the initial stages of AD in the AD group. However, in the current study, there were no differences in rsEEG power among HC and individuals with aMCI. This may be due to individual differences in alterations of brain activity during the pathological aging process (6). Another thing is that EEG recordings with a cognitive task may have better chance to detect cognitive impairments (32). Our group's earlier work demonstrated that when a cognitive task was performed with an oddball paradigm, decreased event-related delta oscillations were found in individuals with AD (33,34,35) and aMCI (36,37,38) compared to HC. Due to the lack of significant differences between HC and aMCI groups, rsEEG measures were not further explored for discriminatory power in the current study. Thus, rsEEG may not provide sufficient sensitivity to detect differences between individuals with aMCI and HC. However, we recommend that future studies investigate event-related potentials and/or oscillations which may provide high accuracy discrimination between individuals with aMCI and HC.

Numerous associations were obtained between electrophysiological parameters and neuropsychological measurements in the current study. For instance, increased delta, and theta power were related to lower MMSE scores in the whole

sample. Several studies reported associations between delta and theta power and MMSE scores (26,39), which is in line with our findings. In addition, associations were also analyzed within each group, and was detected that increase in delta power of AD was related to lower MMSE scores. In previous studies, delta power has been associated with a lower cognitive status in individuals with AD (22, 39), consistent with our findings. The association was proposed to be related with more abnormalities of white-matter integrity and cerebrospinal fluid (CSF) volume in individuals with AD (22,26).

In our study, there were also relationships between delta power and scores of memory, language, and attention/executive functions in the whole sample. In the literature, inconsistent results were reported regarding delta power as it had been detected to have associations with cognition. Vlahou et al. (40) showed that delta power is related to executive functions, and perceptual speed in the healthy elderly. Conversely, Finnigan and Robertson (41) did not state any relationship between neuropsychological measures (recall, attention, executive functions, and delta power). However, in the aforementioned studies, the samples did not individuals with AD nor those with aMCI. In the current study, delta power was associated with cognitive measures in the whole sample. Thus, we could speculate that aMCI and AD groups would affect the associations in a way that lower scores in cognitive measures were related to increased delta power. Moderate associations were also found between theta power and scores in several cognitive domains, indicating higher theta power was related to decrease in attention/executive function and language abilities. This finding is consistent with studies showing a relationship between attention/executive functions and theta power (42,43,44). On each group analyses, increased theta power of individuals with aMCI was found to be associated with lower scores on the language domain. Beese et al. (45) stated that low theta power over central regions increases with age and was related to language abilities. Furthermore, alpha 2 power was detected to be related to language abilities of individuals with MCI. This may be due to the fact that alpha 1 power is more responsible for attention, while alpha 2 power is involved in processing semantic information (46).

Thus, the current study demonstrated significant resting-state electrophysiological changes in individuals with aMCI and AD. Increased delta and theta power were found in the AD group compared to the other groups, while decreased alpha power was only detected in AD compared to the healthy elderly group. We did not detect any differences among individuals with aMCI and the healthy elderly. At this point, it can be only speculated that aMCI group in this study may not include individuals with a risk of progression to AD. Moreover, we can also speculate that rsEEG may not be sensitive enough in comparing individuals with aMCI and healthy elderly, as mentioned earlier. Further studies are recommended to investigate the brain activity of those with aMCI compared to HC via event-related potentials and/or oscillations. The strength of the present study includes using rsEEG and neuropsychological measures to assess alterations in brain activities among individuals with aMCI and AD in relation to the healthy elderly, while trying to adjust for confounding factors. Having relatively small sample size brings about a potential limitation to our study. Another possible limitation is that individuals with AD were not evaluated in terms of CSF biomarkers due to the retrospective design of the current study. Therefore, further studies are required to investigate alterations in brain dynamics in individuals with aMCI and AD of longer duration of the disease using a larger sample size.

Conclusion

We investigated rsEEG power for differentiating individuals with AD from those with aMCI and HC. Our findings revealed altered electrophysiological responses in AD, possibly due to cholinergic deterioration and interruption in the cortico-cortical association pathways. Delta and theta power were also able to differentiate aMCI from AD at high sensitivity and specificity both at a level of 80%. The detected associations between rsEEG power values and the MMSE scores, attention/executive functions, memory, and language domains indicated that delta and theta power may involve different cognitive functions. The clinical implications and significance of the findings are yet to be determined. However, the results of the current study may predict the need for future researchers to interpret neural alterations using rsEEG in individuals with aMCI and AD. Since individuals with aMCI without any CSF markers in the current study may not reflect the prodromal stage of AD, further studies are needed to investigate the criterion validity of the rsEEG spectral power between individuals with AD and those with aMCI through CSF markers in order to evaluate differences in prodromal AD.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained by the Dokuz Eylul University Non-interventional Research Ethics Committee (decision no: 2018/05-09, date: 15.02.2018).

Informed Consent: Written informed consent was collected from all participants or their caregivers.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.K., D.H.G., G.G.Y., Design: Ö.K., D.H.G., D.Y., G.G.Y., Data Collection or Processing: Ö.K., D.H.G., D.Y., Analysis or Interpretation: Ö.K., D.H.G., D.Y., Literature Search: Ö.K., D.H.G., Writing: Ö.K., D.H.G., D.Y., G.G.Y.

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