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Association of plasma amyloid- β oligomerization with theta/beta ratio in older adults

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Background: Oligomeric A β (OA β) is a promising candidate marker for Alzheimer's disease (AD) diagnosis. Electroencephalography (EEG) is a potential tool for early detection of AD. Still, whether EEG power ratios, particularly the theta/alpha ratio (TAR) and theta/beta ratio (TBR), reflect A β burden—a primary mechanism underlying cognitive impairment and AD. This study investigated the association of TAR and TBR with amyloid burden in older adults based on MDS-OA β levels.

Methods: 529 individuals (aged ≥ 60 years) were recruited. All participants underwent EEG (MINDD SCAN, Ybrain Inc., South Korea) and AlzOn™ test (PeopleBio Inc., Gyeonggi-do, Republic of Korea) for quantifying MDS-OA β values in the plasma. EEG variables were log-transformed to normalize the data distribution. Using the MDS-OA β cutoff value (0.78 ng/mL), all participants were classified into two groups: high MDS-OA β and low MDS-OA β .

Results: Participants with high MDS-OA β levels had significantly higher TARs and TBRs than those with low MDS-OA β levels. The log-transformed TBRs in the central lobe ($\beta = 0.161$, $p = 0.0026$), frontal lobe ($\beta = 0.145$, $p = 0.0044$), parietal lobe ($\beta = 0.166$, $p = 0.0028$), occipital lobe ($\beta = 0.158$, $p = 0.0058$), and temporal lobe ($\beta = 0.162$, $p = 0.0042$) were significantly and positively associated with increases in MDS-OA β levels. After adjusting for the Bonferroni correction, the TBRs in all lobe regions, except the occipital lobe, were significantly associated with increased MDS-OA β levels.

Conclusion: We found a significant association of MDS-OA β with TBR in older adults. This finding indicates that an increase in amyloid burden may be associated with an increase in the low-frequency band and a decrease in the relatively high-frequency band.

KEYWORDS

amyloid oligomers, EEG, Alzheimer's disease, cognitive impairment, neurotox

Introduction

Alzheimer's disease (AD) is the most common cause of dementia, accounting for nearly 60–80% of all dementia cases. Clinically, AD is characterized by impairments in cognition and daily functioning (Deture and Dickson, 2019). Pathologically, the onset and progression of AD are characterized by the abnormal accumulation of amyloid- β ($A\beta$) plaques and neurofibrillary tangles in the brain (Beason-Held et al., 2013).

Oligomeric $A\beta$ ($OA\beta$) is a promising candidate marker for AD diagnosis (Youn et al., 2019). Serial cleavage of amyloid precursor proteins by β - and γ -secretase generates $A\beta$, first in its oligomeric and fibrous forms, ultimately leading to the generation of amyloid plaques (Sinha and Lieberburg, 1999). Among these, $OA\beta$ is the major neurotoxic species that leads to the development of AD (Tolar et al., 2021). Multimer Detection System- $OA\beta$ (MDS- $OA\beta$), a blood test designed for detecting AD, measures the oligomerization tendency of amyloid- β in the blood. Accumulating evidence has demonstrated that MDS- $OA\beta$ levels are significantly associated with the presence and severity of cognitive impairment and that this association is stronger than that observed for $A\beta$ plaques (Wang et al., 2017; Babapour Mofrad et al., 2021; Dominguez et al., 2022; Kim et al., 2022). Wang et al. (2017) reported that MDS- $OA\beta$ levels were well correlated with clinically used biomarkers of AD and exhibited good sensitivity (78.3%) and specificity (86.5%) in discrimination AD from healthy control cases. Another study noted that MDS- $OA\beta$ yielded good diagnostic accuracy (area under the curve [AUC]: 0.84–0.87) in distinguishing AD from control cases (Jeong, 2004; Wang et al., 2017; Colom-Cadena et al., 2020). In yet another study, MDS- $OA\beta$ levels could be used to identify individuals with abnormal amyloid PET findings, with an AUC of 0.77, which increased to 0.86 when combined with age and APOE4 status. Collectively, these data suggest that plasma MDS- $OA\beta$ is a biomarker of brain amyloidosis (Jeong, 2004; Wang et al., 2017; Colom-Cadena et al., 2020; Babapour Mofrad et al., 2021; Dominguez et al., 2022; Kim et al., 2022).

Electroencephalography (EEG) is a noninvasive neuroimaging technique used to measure and record postsynaptic dendritic currents in synchronized cortical neurons (Frisoni et al., 2010). EEG has emerged as a potential tool for detecting aberrant neuronal activity associated with cognitive impairment and AD (Frisoni et al., 2010). Numerous lines of evidence have validated the possibility of using EEG for early detection of AD, reporting neural alterations in patients with AD such as decreased alpha and beta rhythm activity along with increased delta and theta oscillations (Babiloni et al., 2016; Cassani et al., 2018; Min et al., 2022). Ranasinghe et al. (2022) has shown that alpha and beta can be affected totally inverse way by amyloid accumulation and tau accumulation. Interestingly, in recent studies, EEG power ratios between fast and slow activities have been used to achieve good discrimination between different stages of AD (Bennys et al., 2001). Among these ratios, the theta/alpha ratio (TAR) and theta/beta ratio (TBR) are considered the most promising indices for AD diagnosis (Shulman and Goldstein, 2014; Tsolaki et al., 2014; Tzamourta et al., 2019). TAR can be sensitive and specific marker in early onset AD patients (Özbek et al., 2021). Significant differences

in the distribution of TAR and TBR have been observed between AD and healthy control groups, and multiple studies have documented an obvious visual separation between AD and healthy control groups with increasing window durations (Shulman and Goldstein, 2014; Tsolaki et al., 2014; Tzamourta et al., 2019). The results of these studies support the notion that TAR and TBR are potential markers for distinguishing patients with AD from controls (Brenner et al., 1986; Bennys et al., 2001).

Synaptic dysfunction and loss are fundamental to the pathological cognitive decline observed in AD (Colom-Cadena et al., 2020). Studies on human and mouse models have demonstrated that aggregated $A\beta$ plaques are associated with local synapse loss, as well as losses in memory and synaptic plasticity (Koffie et al., 2012; Jackson et al., 2016), downstream of amyloidosis. EEG parameters represent changes in neuronal and synaptic dysfunction (Frisoni et al., 2010); however, it remains unknown whether EEG power ratios, particularly TAR and TBR, reflect $A\beta$ burden—a major pathological mechanism underlying cognitive impairment and AD. Based on this circumstantial evidence, we hypothesized that elevation of TAR or TBR (i.e., the ratio of the increased relative power in the low-frequency band to the reduced relative power in the high-frequency band) is associated with a high amyloid burden. To examine this hypothesis, we investigated the association of TAR and TBR with amyloid burden in older adults, based on MDS- $OA\beta$ levels.

Methods

Study population

Between January and October 2022, 529 individuals (aged ≥ 60 years) were recruited from the Department of Neurology at the Veterans Health Service Medical Center in Seoul, Korea. All participants completed a neuropsychological test battery and underwent blood tests related to cognitive function, including the following: total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol; triglycerides, free T4; thyroid stimulating hormone (TSH); and vitamin B12. A medical specialist interviewed all participants prior to each diagnosis.

The inclusion criteria were as follows: (a) self-report of cognitive decline; (b) ability to independently complete the clinical tests and questionnaires, and (c) voluntary agreement to participate in the study. The exclusion criteria were as follows: (a) diagnosis of brain infarction, cerebral hemorrhage, or Parkinson's disease; and (b) diagnosis of another serious disease (e.g., cancer or mental illness). Experienced neurologic clinicians evaluated each patient based on the inclusion and exclusion criteria. The study protocols were approved by the Institutional Ethical Review Board of the Veterans Health Service Medical Center (BOHUN 2021–02–024, BOHUN 2022–05–006, BOHUN 2022–01–019).

The recruited participants underwent EEG and plasma MDS- $OA\beta$ measurements and completed baseline questionnaires (age, sex, education level, and assessments of depressive symptoms). A total of 529 individuals volunteered to participate in the study and provided informed consent upon enrollment. Of these, 102 participants subsequently dropped out of the study owing to incomplete responses related to diseases listed as exclusion criteria and refusal to undergo

EEG or blood collection during examination. Thus, 427 individuals were eligible for inclusion.

MDS-OA β assay description and procedure

The AlzOn™ test (PeopleBio Inc., Gyeonggi-do, Republic of Korea) was employed to quantify MDS-OA β values in the plasma samples from the subjects (An et al., 2017). This assay relies on the Multimer Detection System (MDS), a modified enzyme-linked immunosorbent assay (ELISA) that utilizes epitope-overlapping antibodies specific to the N-terminus of A β for the selective detection of A β oligomers over monomers in samples (An et al., 2010). Specifically, we used mouse monoclonal antibody 6E10 (BioLegend, San Diego, CA, United States) as the capturing antibody and WO2-HRP antibody (Absolute Antibody Ltd., Oxford, United Kingdom) as the detection antibody.

Blood samples were collected in BD vacutainer heparin tubes and centrifuged at 1500 X g for 10 min within 2 h of sampling. The obtained plasma was immediately aliquoted and stored at -80°C until analysis. Prior to the assay, aliquots of plasma samples were thawed at room temperature for 15 min. Following the assay protocol of the AlzOn™ test, HAMA blocker and PBR-1 (synthetic A β made by PeopleBio Inc.) was spiked into the plasma, and the mixture was incubated at 37°C for 48 h. The plasma sample mixture and serially diluted OA β standards were then added to each well of 96-well plates precoated with capturing antibody and incubated at room temperature for 1 h. After washing the plates three times with washing buffer, HRP-conjugated detection antibody solution was added to the wells, and the plates were incubated for an additional hour at room temperature. Following another three washes with washing buffer, an enhanced chemiluminescence substrate solution was added, and the Relative Luminescence Unit (RLU) signal was measured using a microplate reader. Dilutions that provided signals within the linear range of the standard curves were used to convert RLU values into concentrations of oligomeric A β .

Acquisition and analysis of EEG data

EEG assessments were conducted over 5 min in a quiet and soundproof room with dim lighting. The participants were in a comfortable resting state with their eyes closed. The EEG equipment used was a Ybrain MINDD-SCAN system (YEP-119B) with 19 channels and linked ears, which served as reference positions: Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2. The impedance between the skin and all electrodes was consistently maintained at 5 k Ω or less. The sampling frequency was set to 500 Hz, and the resolution of the analog-to-digital converter was 24-bit. The collected data were stored and preserved in the European Data Format (EDF).

All preprocessing steps and analyses were conducted using Python (version 3.8.12). The EDF files were loaded using pyEDFlib (version 0.1.30), and the data recorded after the initial 5 s were processed using MNE (version 0.19.2). Basic filtering of the raw data was performed using an MNE notch filter (target: 60 Hz, notch width: 3 Hz) and a band-pass filter (low cutoff frequency: 1.3 Hz, high cutoff frequency: 60 Hz). Furthermore, a flat-line rejection and Random Sample

Consensus (RANSAC) algorithm was applied to detect outliers and remove noisy channels.

The signal, which was now free of noise due to preprocessing, was converted to the frequency domain. The size of each band (delta: 1–4 Hz, theta: 4–8 Hz, alpha: 8–12 Hz, beta: 12–25 Hz, high beta: 25–30 Hz, gamma: 30–40 Hz) was averaged and multiplied by the size of the frequency range to calculate the absolute band power (uV²). To correct for individual deviations in absolute band power due to differences in impedance between the electrode and scalp during measurement, the relative band power (%) was calculated by dividing each band by the sum of all absolute bands. The band power ratios were calculated by dividing the values by the band power (DAR: delta/alpha ratio, TAR, TBR). The TAR and TBR were thus obtained by dividing the theta band power density by the alpha or beta band power density for each channel. The mean lobar TAR and TBR were defined as the sum of the corresponding channels in each lobe: FP1, FP2, F3, F4, F7, F8, and Fz leads for the frontal lobe; C3, C4, and Cz leads for the central lobe; T3, T4, T5, and T6 leads for the temporal lobe; P3, P4, and Pz leads for the parietal lobe; and O1 and O2 leads for the occipital lobe.

Neuropsychological test

We used the brief version of the Seoul Neuropsychological Screening Battery (SNSB), named the SNSB-Core (SNSB-C), to evaluate cognitive performance (Kang et al., 2015). All participants completed tests including the Korean version of Boston Naming Test, Rey Complex Figure Test, Seoul Verbal Learning Test-Elderly's version, Digit Symbol Coding, the Korean version of Color Word Stroop Test, Controlled Oral Word Association Test, and Korean-Trail Making Test-Elderly's version.

Statistical analysis

Using the MDS-OA β cutoff value (0.78 ng/mL), all participants were classified into two groups: high MDS-OA β (≥ 0.78 ng/mL) and low MDS-OA β (< 0.78 ng/mL) (Youn et al., 2020). The EEG indices (TAR and TBR) were log-transformed to normalize the data distribution. The Shapiro–Wilk normality test had a value of p greater than 0.05, which indicated normal distribution of data. Plasma levels of MDS-OA β and the log-transformed EEG power ratio (TAR and TBR) in the five lobar regions (central, frontal, parietal, occipital, and temporal lobes) were compared between the two groups using t -tests. The correlation coefficients between plasma MDS-OA β levels and the TAR and TBR in each of the five lobes were calculated using Pearson's correlation analysis. We performed multiple linear regression to estimate the association between the log-transformed TAR or TBR in each lobe and plasma MDS-OA β levels, with beta coefficients and standard error (SE) of the EEG power ratios. The regression models were adjusted for age, sex, and education level. In addition, we adjusted the Bonferroni correction to control the overall probability of a Type I error for multiple hypothesis tests.

All analyses were performed using Statistical Analysis System version 9.2 (SAS Institute, Cary, NC, United States), and the level of statistical significance was set at $p \leq 0.05$.

TABLE 1 Characteristics of the study population unit: *n* (%).

	Total population		MDS-OA β (ng/mL)				<i>p</i> -value
			Low (<0.78)		High (\geq 0.78)		
60–64	21	(4.92)	11	(4.95)	10	(4.88)	0.0109
65–69	41	(9.60)	26	(11.71)	15	(7.32)	
70–74	127	(29.74)	67	(30.18)	60	(29.27)	
75–79	165	(38.64)	94	(42.34)	71	(34.63)	
80–84	58	(13.58)	18	(8.11)	40	(19.51)	
\geq 85	15	(3.51)	6	(2.70)	9	(4.39)	
Mean (SD) of Age	74.9	(5.30)	74.4	(5.02)	75.4	(5.55)	0.0413
Female	189	(44.26)	88	(39.64)	101	(49.27)	0.0454
Male	238	(55.74)	134	(60.36)	104	(50.73)	
Education level							
Below middle school	186	(43.56)	93	(41.89)	93	(45.37)	0.7696
High school	116	(27.17)	62	(27.93)	54	(26.34)	
Over college	125	(29.27)	67	(30.18)	58	(28.29)	
Mean (SD) of Education year 10.7	10.7	(4.46)	10.9	(4.41)	10.5	(4.51)	0.3658

Results

Table 1 presents the characteristics of the overall study population and the two MDS-OA β groups. Among the 427 participants, those age 75–79 accounted for the largest proportion (38.64%), and their average age was 74.9 years old. The proportion of male (55.74%) was higher than that of female. A high proportion of participants had below middle school education (43.56%), and the average number of educational years was 10.7 years. There were significant differences in age ($p=0.0109$) and sex ($p=0.0454$) between the low and high MDS-OA β groups. In the low MDS-OA β group, a high proportion of participants were 75–79 years old ($n=94$; 42.34%), male ($n=134$; 60.36%), and had below middle school education ($n=93$; 41.89%). Their average age and educational year were 74.4 and 10.9 years, respectively. In the high MDS-OA β group, a high proportion of participants were 75–79 years old ($n=71$; 34.63%), male ($n=104$; 50.73%), and had below middle school education ($n=93$; 45.37%). Their average age and educational year were 75.4 and 10.5 years, respectively.

Table 2 shows the mean (SD) of neuropsychological test scores according to MDS-OA β cutoff value (0.78 ng/mL). The cognitive performance of older participants in the low MDS-OA β group was significantly lower than that of the high MDS-OA β group (all value of $p<0.0001$); 71.63 vs. 57.97 for Boston naming test, 48.44 vs. 24.80 for Rey copy test, 64.87 vs. 42.35 for Short-term verbal learning test, 73.18 vs. 50.24 for Digit symbol coding, 70.16 vs. 50.24 for Trail Making Test A, 73.65 vs. 56.64 for Trail Making Test B, and 62.91 vs. 35.83 for Color Word Stroop Test. Significant differences existed in Controlled Oral Word Association Test scores between the low and high MDS-OA β groups. In particular, the score difference in the Controlled Oral Word Association Test (Animal+'-') between the two groups (66.42 vs. 38.44) was considerable.

Table 3 shows the mean (SD) MDS-OA β levels according to various characteristics of the study population. The mean MDS-OA β

level was elevated among older participants, female, and those with low education levels. In the low MDS-OA β group, MDS-OA β levels were higher in age 70–74 years, men, and older adults with below middle school education. In the high MDS-OA β group, relatively higher MDS-OA β levels were more likely for older participants, m, and those with low education levels.

Table 4 shows the comparison of arithmetic mean (SD) EEG power ratios between the high and low MDS-OA β groups according to lobar regions. In the total population, the TAR was highest in the frontal lobe (mean = 1.003, SD = 1.79), as was the TBR (mean = 0.821, SD = 1.80). Participants with high MDS-OA β levels had higher mean TARs in all lobar regions than those with low MDS-OA β levels, but there was no significant difference in TARs between them. In all lobar regions, the high MDS-OA β group had a higher mean (SD) TBR than the low MDS-OA β group: 0.843 (1.95) vs. 0.767 (1.74) in the central lobe ($p=0.0068$), 1.041 (1.90) vs. 0.969 (1.68) in the frontal lobe ($p=0.0020$), 0.840 (1.99) vs. 0.743 (1.82) in the parietal lobe ($p=0.0442$), 0.902 (2.06) vs. 0.800 (1.82) in the occipital lobe ($p=0.0058$), and 0.881 (2.06) vs. 0.778 (1.79) in the temporal lobe ($p=0.0044$). Table 5 shows the correlation coefficients between the log-transformed EEG power ratio and MDS-OA β by lobar regions. The correlation coefficients for the TBR were statistically significant in the central lobe ($r=0.133$; $p=0.0061$), frontal lobe ($r=0.122$; $p=0.0117$), parietal lobe ($r=0.132$; $p=0.0064$), occipital lobe ($r=0.122$; $p=0.0114$), and temporal lobe ($r=0.135$; $p=0.0053$); however, there were no significant correlations for the TAR. After adjusting for the Bonferroni correction, the log-transformed EEG power ratio was not significantly correlated.

Table 6 shows the linear regression coefficients (SE) for log-transformed EEG power ratios associated with increased MDS-OA β levels. The regression coefficient of the TAR was not significant for any lobar region. In contrast, the TBRs in the central lobe ($\beta=0.161$, $p=0.0026$), frontal lobe ($\beta=0.145$, $p=0.0044$), parietal lobe ($\beta=0.166$, $p=0.0028$), occipital lobe ($\beta=0.158$, $p=0.0058$), and temporal lobe (beta = 0.162,

TABLE 2 Mean (SD) of neuropsychological test scores between the low and high MDS-OA β groups.

Neuropsychological assessment	MDS-OA β (ng/mL)				p-value
	Low (<0.78)		High (\geq 0.78)		
	Mean	SD	Mean	SD	
Boston naming test	71.63	(21.94)	57.97	(29.67)	<0.0001
Rey copy score	48.44	(19.39)	24.80	(23.58)	<0.0001
Short-term verbal learning test	64.87	(23.84)	42.35	(30.93)	<0.0001
Digit symbol coding	73.18	(22.99)	50.24	(28.89)	<0.0001
Controlled Oral Word Association Test					
- Animal	59.56	(24.37)	38.26	(29.34)	<0.0001
- '↵'	67.21	(25.83)	43.41	(28.08)	<0.0001
- Animal+'↵'	66.42	(21.70)	38.44	(27.59)	<0.0001
Trail Making Test A	70.16	(17.83)	58.45	(24.06)	<0.0001
Trail Making Test B	73.65	(14.24)	56.64	(25.22)	<0.0001
Color Word Stroop Test	62.91	(25.12)	35.83	(27.66)	<0.0001

TABLE 3 Mean (SD) MDS-OA β by characteristics of the study population.

	Total population		MDS-OA β (ng/mL)			
			Low (<0.78)		High (\geq 0.78)	
Age						
60–64	0.667	(0.30)	0.417	(0.21)	0.924	(0.09)
65–69	0.688	(0.31)	0.493	(0.20)	1.011	(0.13)
70–74	0.753	(0.27)	0.551	(0.19)	0.987	(0.14)
75–79	0.702	(0.29)	0.504	(0.21)	0.965	(0.14)
80–84	0.836	(0.30)	0.476	(0.22)	0.993	(0.15)
\geq 85	0.825	(0.25)	0.521	(0.21)	0.960	(0.12)
Sex						
Female	0.760	(0.28)	0.519	(0.19)	0.971	(0.28)
Male	0.718	(0.30)	0.505	(0.21)	0.980	(0.30)
Education level						
Below middle school	0.752	(0.28)	0.534	(0.19)	0.975	(0.14)
High school	0.719	(0.31)	0.475	(0.20)	0.982	(0.15)
Over college	0.731	(0.29)	0.511	(0.22)	0.970	(0.13)

MDS-OA β : Multimer Detection System-Oligomeric Amyloid- β .

$p = 0.0042$) were significantly and positively associated with increases in MDS-OA β levels. This association remained after adjusting for age, sex, and education level. After adjusting for the Bonferroni correction, the TBRs in all lobe regions, except the occipital lobe, were significantly associated with increased MDS-OA β levels. Figure 1 displays the linear regression plots for the association of TAR and TAB in all lobar regions with MDS-OA β levels.

Discussion

Our analysis revealed a significant association of MDS-OA β with log-transformed EEG power ratios, TBR, among older adults.

Specifically, individuals in the high MDS-OA β group had significantly higher TBRs in the central, frontal, parietal, and temporal lobes than those in the low MDS-OA β group. The observed association of MDS-OA β with TBR indicates that an increase in amyloid burden may be associated with an increase in the low-frequency band and a decrease in the relatively high-frequency band.

AD is caused by the loss of synaptic junctions due to the accumulation of neurotoxic A β in the brain, and synaptic dysfunction is known to represent the best anatomical relationship for early cognitive impairment (Coben et al., 1985). In the amyloid cascade hypothesis, A β monomers are aggregated to form soluble A β oligomers (Babapour Mofrad et al., 2021). Some oligomers aggregate into amyloid plaques, while others cause neuronal damage, leading to dementia (Yagami, 2006). Among the various types of A β , OA β is the most neurotoxic, and a strong correlation

TABLE 4 Arithmetic mean (SD) of EEG power ratios between the high and low MDS-OAβ groups, according to lobar regions.

EEG parameters	Total population		MDS-OAβ (ng/mL)				p-value
			Low (<0.78)		High (≥0.78)		
Theta-Alpha ratio							
Central lobe	0.802	(1.85)	0.645	(1.86)	0.742	(1.82)	0.5977
Frontal lobe	1.003	(1.79)	0.778	(1.80)	0.870	(1.78)	0.7549
Parietal lobe	0.788	(1.91)	0.554	(1.94)	0.644	(1.97)	0.7381
Occipital lobe	0.847	(1.94)	0.523	(2.00)	0.615	(2.04)	0.6826
Temporal lobe	0.826	(1.91)	0.680	(1.76)	0.768	(1.81)	0.4411
Theta-Beta ratio							
Central lobe	0.690	(1.85)	0.767	(1.74)	0.843	(1.95)	0.0068
Frontal lobe	0.821	(1.80)	0.969	(1.68)	1.041	(1.90)	0.0020
Parietal lobe	0.596	(1.96)	0.743	(1.82)	0.840	(1.99)	0.0442
Occipital lobe	0.566	(2.02)	0.800	(1.82)	0.902	(2.06)	0.0058
Temporal lobe	0.721	(1.79)	0.778	(1.79)	0.881	(2.03)	0.0044

MDS-OAβ: Multimer Detection System-Oligomeric Amyloid-β. EEG power ratios were log transformed.

TABLE 5 Correlation coefficients between the EEG power ratio and MDS-OAβ, according to lobar regions.

EEG parameters	r	p-value
Theta-Alpha ratio		
Central lobe	0.063	0.1972
Frontal lobe	0.047	0.3358
Parietal lobe	0.063	0.1969
Occipital lobe	0.060	0.2167
Temporal lobe	0.059	0.2235
Theta-Beta ratio		
Central lobe	0.133	0.0061
Frontal lobe	0.122	0.0117
Parietal lobe	0.132	0.0064
Occipital lobe	0.122	0.0114
Temporal lobe	0.135	0.0053

MDS-OAβ: Multimer Detection System-Oligomeric Amyloid-β. EEG power ratios were log transformed.

TABLE 6 Linear regression coefficients for EEG power ratio associated with increased MDS-OAβ levels, according to lobar regions.

EEG parameters	Unadjusted model			Adjusted model ^a		
	β	(SE)	p-value	β	(SE)	p-value
Theta-Alpha ratio						
Central lobe	0.058	(0.06)	0.3007	0.044	(0.05)	0.4219
Frontal lobe	0.038	(0.05)	0.4682	0.031	(0.05)	0.5465
Parietal lobe	0.074	(0.06)	0.2258	0.046	(0.06)	0.4383
Occipital lobe	0.065	(0.06)	0.3076	0.044	(0.06)	0.4790
Temporal lobe	0.063	(0.05)	0.2277	0.046	(0.05)	0.3769
Theta-Beta ratio						
Central lobe	0.170	(0.05)	0.0020	0.161	(0.05)	0.0026
Frontal lobe	0.154	(0.05)	0.0030	0.145	(0.05)	0.0044
Parietal lobe	0.181	(0.06)	0.0018	0.166	(0.06)	0.0028
Occipital lobe	0.159	(0.06)	0.0073	0.158	(0.06)	0.0058
Temporal lobe	0.175	(0.06)	0.0025	0.162	(0.06)	0.0042

MDS-OAβ: Multimer Detection System-Oligomeric Amyloid-β. EEG power ratios were log transformed. Significant p-values after the Bonferroni correction are marked in bold.

^aAdjusted by age, sex, and education level.

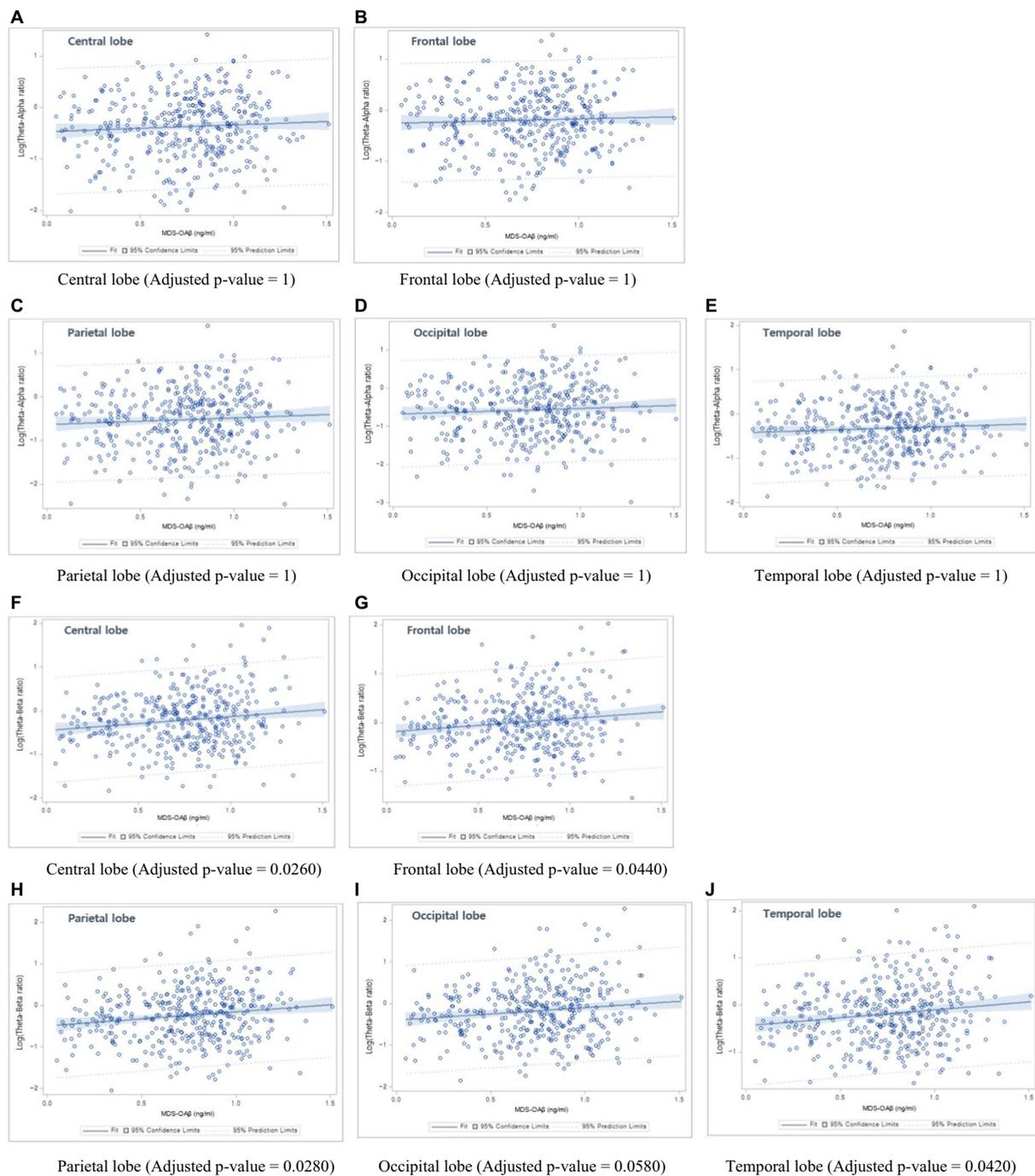


FIGURE 1 Linear regression plots. (1) Association between Theta-Alpha ratio and MDS-OA β levels: (A) Central lobe, (B) Frontal lobe, (C) Parietal lobe, (D) Occipital lobe, and (E) Temporal lobe; (2) Association between Theta-Beta ratio and MDS-OA β levels: (F) Central lobe, (G) Frontal lobe, (H) Parietal lobe, (I) Occipital lobe, and (J) Temporal lobe.

has been observed between its presence and the severity of cognitive symptoms, compared to the A β plaque burden (Meng et al., 2019; Babapour Mofrad et al., 2021). A β plaques deposited in the temporal neocortex in the early stages of AD interfere with neural circuits connecting the prefrontal cortex (Miao et al., 2021). Theta oscillations have been shown to orchestrate communication between prefrontal region and the hippocampus. Activation of the default mode network is inversely related to theta oscillations, and under-activation of the default mode network due to a high amyloid load ultimately results in

hyperactivation of the midfrontal theta band (Schmidt et al., 2013). That is, an increase in theta and delta activity and a decrease in alpha and beta activity have been observed in the context of AD (Ingelsson et al., 2004; Sheng et al., 2012; Tsolaki et al., 2014; Walsh et al., 2017). Schmidt et al. (2013) identified a lower alpha/theta ratio in early and moderate stages of AD, indicating a pattern of increased theta and decreased alpha activity in patients with AD (Brenner et al., 1986). Previous studies have also demonstrated that patients with AD exhibit decreased beta power and increased theta power when compared with

controls. Therefore, increased TAR and TBR values may be indicative of AD (Sheline et al., 2010).

Several studies have investigated the relationship between cerebrospinal fluid (CSF) biomarkers representing amyloid accumulation and changes in qEEG power spectral patterns. In one such study of 33 patients, Campbell et al. (2021) reported that the p-tau/A β 42 and t-tau/A β 42 ratios were strongly associated with increased relative theta power and reduced cognitive speed. A cross-sectional study of the INSIGHT-preAD cohort found increased theta band power in the middle prefrontal cortex in individuals with large amyloid deposits, relative to that observed in those with small amyloid deposits. This evidence suggests that theta power increase, one of the prominent markers of 'EEG slowing', is correlated with cortical amyloid deposition (Spinelli et al., 2022).

Our data are consistent with these findings and provide new insight, suggesting that increases in both TAR and TBR reflect A β pathology. These EEG changes may reflect amyloid-based hypoactivation of the default-mode network (Babiloni et al., 2018). Notably, we observed no significant association with A β oligomerization in the alpha band, a frequency strongly associated with AD progression. Our results suggest that TBR may be a better indicator than TAR. The MDS-OA β method may reflect AD-induced changes in EEG; in particular, TBR may be more closely related to the amyloid burden.

The mechanism underlying the relationship between A β 42 and slowing of EEG activity may be explained by cholinergic deficits. AD begins with alterations in signaling systems, including the cholinergic pathways. Studies in cultured rat cortical cells have demonstrated that amyloid peptides selectively impair the muscarinic cholinergic receptor-mediated signaling pathway (Spinelli et al., 2022). A β interferes with the mechanisms leading to uncoupling of muscarinic receptors and negatively affects acetylcholine synthesis and release. Decreased cortical cholinergic activity increases slow EEG activity (Huang et al., 2000). The negative effect of A β on cholinergic transmission in the brain can increase slow frequency activity (Spehlmann and Norcross, 1982; Visser et al., 2009). Alpha and beta waves are mainly generated in the cortex and propagate through connections within the cortex. Thus, brain atrophy in patients with AD may explain the rapid decline in the EEG rhythm (Smailovic et al., 2018). We hypothesize that decreased cholinergic activity, increased theta activity, and decreased beta activity due to brain atrophy are associated with the amyloid oligomerization pattern.

This study had several limitations. First, this study is based on cross-sectional, observational design. Second, while the biomarkers for brain amyloid have been well-established in cerebrospinal fluid amyloid- β 42 (A β 42) (CSF A β 42) and PET amyloid imaging, amyloid burden in our data was only based on plasma MDS-OA β levels. MDS-OA β is not a thoroughly validated marker for AD. However, owing to the high neurotoxicity of oligomerized A β , it has demonstrated a robust correlation with other clinical biomarkers, including CSF A β 42 and amyloid PET. Third, the *r*-values of 0.133 indicate fairly weak correlation, but it's still significant the value of conducting qEEG to detect toxic amyloid burden early in order to reduce the risk of AD. Longitudinal studies are necessary to confirm whether the TBR have prognostic potential for amyloid accumulation with amyloid PET imaging. Moreover, our population was individuals aged ≥ 60 years visited at the Department of neurology in a single medical center. Selection bias may be unavoidable, and our results cannot be generalized. Future work is needed to confirm the observed association from a representative sample and to reduce the uncertainty.

In conclusion, we found a significant association of MDS-OA β with TBR among older adults. Increases in TBR were predominant among individuals with plasma MDS-OA β levels. This contributes to research into EEG power ratio as a potential marker of AD, specifically linked to A β burden.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Veterans Health Service Medical Center (IRB No. BOHUN 2021-02-024, BOHUN 2022-05-006, BOHUN 2022-01-019). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

HB: Conceptualization, Methodology, Resources, Writing – original draft. MK: Methodology, Resources, Validation, riting – review & editing. S-WH: Investigation, Resources, Validation, Writing – review & editing. D-EJ: Data curation, Investigation, Resources, Writing – review & editing. KL: Data curation, Formal analysis, Resources, Software, Writing – review & editing. SL: Data curation, Formal analysis, Software, Writing – review & editing. J-YM: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft. K-BM: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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