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ORIGINAL RESEARCH

Therapeutic Potential of Porcine Brain-Derived Peptide Mixture (PBDP) in Alzheimer's Disease: An Exploratory Study on Quantitative Electroencephalography (qEEG) Changes

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Background: This exploratory study investigates the therapeutic potential of Porcine Brain-Derived Peptide Mixture (PBDP) in Alzheimer's Disease (AD) by examining changes in quantitative electroencephalography (qEEG) parameters following treatment.

Methods: We analyzed qEEG data from 27 AD patients treated with 2-weeks of PBDP treatment and compared them to a control group of 20 patients at 2-month follow-up, all of whom were previously on donepezil therapy.

Results: EEG modifications were noted within two weeks of PBDP administration, including improvements in EEG patterns such as reduced Theta/Beta (4.437 ± 3.979 to 3.859 ± 3.587, $p = 0.442$), Theta/Alpha ratio (1.815 ± 1.637 to 1.578 ± 1.304, $p < 0.05$), and Delta/Alpha ratio (2.365 ± 2.471 to 2.105 ± 2.402, $p < 0.05$) across various brain regions, suggesting enhanced cortical activity. Post-intervention, 55% of patients showed caregiver-reported improvements in mood and daily activities.

Conclusion: PBDP could serve as a viable therapeutic approach for managing AD, and qEEG could serve as a monitoring biomarker for acute drug effects, warranting further investigation into its long-term benefits and mechanistic pathways.

Keywords: Alzheimer's disease, brain-derived neurotrophic factor, quantitative electroencephalography, porcine brain-derived peptide mixture, power spectral density

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder debilitating condition severely impairs cognitive functions, ultimately compromising an individual's ability to perform everyday tasks. The disease progression is often accompanied by a gradual decline in memory, language skills, problem-solving abilities, and other critical brain functions. It is characterized by the accumulation of amyloid-beta plaques and neurofibrillary tangles in the brain, leading to neuronal death and cognitive decline.[1] This degenerative pathology primarily affects regions of the brain associated with memory and cognition, such as the hippocampus and cortex. Despite considerable advancements in understanding the pathological mechanisms underlying AD, effective therapeutic strategies that can halt or reverse the progression of this disease are still lacking.

Brain-derived neurotrophic factor (BDNF), a protein found in abundance in these areas of the brain, plays a critical role in maintaining neuronal health. BDNF belongs to a family of proteins known as neurotrophins, which support neuron survival, promote growth and differentiation of new neurons and synapses, and enhance synaptic plasticity - all

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vital for learning and memory.[2] In AD, there is often a significant reduction in BDNF levels, which has been associated with impaired synaptic function and neuronal loss.[3,4] The exact mechanisms underlying this reduction are not fully understood but may be related to increased amyloid-beta levels that can cause reduced BDNF gene expression.[5] While enhancing BDNF signaling has been suggested as a potential therapeutic strategy to mitigate some of the neuronal damage associated with AD pathology,[6–9] its role in directly counteracting disease progression remains an area of active investigation. The strategies aimed at boosting BDNF activity could potentially serve as another effective therapeutic approaches for managing or even reversing some aspects of AD progression.

The pharmacological mechanism of Porcine Brain-Derived Peptide Mixture (PBDP), a peptide-based medication, is gaining attention due to its potential neuroprotective and neurotrophic effects that parallel the function of BDNF.[10] PBDP is a unique composite of neurotrophic peptides derived from pig brains. This blend includes pivotal factors such as BDNF, Glial Cell Line-Derived Neurotrophic Factor (GDNF), Nerve Growth Factor (NGF), and Ciliary Neurotrophic Factor (CNTF).[11] These neurotrophins are recognized for their critical roles in neuronal survival, development, and function by activating TrkB and other receptor-mediated signaling pathways.[12,13] In addition to these neurotrophic factors, Sonic Hedgehog (Shh) signaling pathway is a critical regulator of many aspects of neural development and regeneration.[14] The Sonic Hedgehog pathway plays an instrumental role not only for normal brain development but also maintaining adult brain homeostasis including processes like neural stem cell proliferation.[15,16]

Several clinical trials have demonstrated the efficacy of PBDP in alleviating cognitive deficits and enhancing functional performance among patients with mild-to-moderate AD.[17–20] Our exploratory research aims to investigate the potential effects of certain neurotrophic peptides on quantitative electroencephalography (qEEG) of patients with AD.

This study focuses on evaluating changes after PBDP injection therapy among AD patients focusing on parameters such as quantitative qEEG. Research has shown that AD is associated with specific changes in EEG patterns, including slowing of the dominant rhythm, increased delta and theta band power, and decrease alpha and beta band power.[21,22] These changes have been found to correlate with cognitive decline, making EEG a potentially useful tool for monitoring disease progression[23,24] and response to treatment.[22,25] Furthermore, studies have demonstrated that qEEG measures can detect changes in brain function induced by pharmacological interventions. For instance, drugs known to enhance cognitive function have been found a tendency to increase alpha and beta power and decrease theta power on qEEG recordings.[25–27] In addition, several studies have shown that qEEG measures are sensitive enough to detect differences between responders and non-responders to AD medication.[28,29] This suggests that qEEG could be used as an early marker of treatment response. The use of qEEG as a tool to evaluate drug effects in patients with AD has gained significant attention over the years. qEEG, a non-invasive method for recording electrical activity in the brain, provides objective and quantifiable data that can be used to assess cerebral function.[30] Therefore, incorporating qEEG into clinical trials could provide valuable insights into new drugs for AD. It could also help identify potential responders early in the course of treatment. In this study, we aim at evaluating changes after PBDP injection therapy among Alzheimer's patients focusing on parameters such as EEG power spectrum.

Methods

Participants

This study was retrospectively conducted on patients registered in the CAU dementia registry (IRB registration No. 2009–005-19331) who underwent electroencephalography (EEG) before and after PBDP administration. The dementia registry is a database of neuropsychological tests, EEGs, and brain imaging data obtained during the diagnostic process for patients presenting with cognitive impairment. Participants were selected from the CAU dementia registry between Jan 1st 2017 and Dec 31st 2020, comprising a treatment group of 27 individuals who received PBDP and a control group of 20 individuals. Informed consent was waived by the Institutional Review Board of Chung-Ang University Hospital due to the retrospective nature of the study. All individuals included in this study were clinically diagnosed with mild-to-moderate AD based on established diagnostic criteria.[31,32] Both intervention and control groups had been consistently administered donepezil for a period exceeding three months. Despite this, they were chosen as subjects due to their progressively worsening conditions. Progressive worsening of condition was defined based on reports of decreased function in daily activities provided by a caregiver or clinician at baseline assessment.

Table 1 Demographic Features of the Participants

	Intervention (n = 27)	Control (n = 20)
Age (avg ± std)	73.12 ± 7.03	72.74 ± 5.4
(range)	57-86	65-82
Male/Female	10/17	4/16
Education years (avg ± std)	8.63 ± 7.23	8.72 ± 4.33
MMSE (avg ± std)	13.0 ± 11.63	15.0 ± 8.7
CDR SOB (avg ± std).	1.7 ± 1.76	1.7 ± 1.8

EEGs were performed at two-month intervals to monitor these patients. Additionally, some of them were administered PBDP as part of their treatment regimen.

The participants had been administered a dosage of 10 cc per day, five days a week for a duration of two weeks. The age of the participants varied, with an average age of 73.12 ± 7.03. The gender distribution was evenly split with 17 females and 10 males in the treatment group. In the control group, the average age was slightly lower at 72.74 ± 5.4, with a gender distribution of 4 males and 16 females. Their detailed demographics were shown in Table 1. There was no significant statistical different feature.

Both intervention and control groups had EEGs performed at baseline and at 2-month follow-up. The intervention group received a two-week course of PBDP treatment starting shortly after baseline EEG, while the control group received no additional intervention during this period. EEG power spectra were compared between baseline and 2-month follow-up in both groups to assess the effects of PBDP treatment. The intervention group also did Multimer Detection System-Oligomeric Amyloid-β (MDS-OAβ) which is a blood-based biomarker for AD. It is a modified sandwich immunoassay for measuring Aβ oligomerization tendency in the plasma.[33,34]

EEG Data Processing

The EEG recording and analysis conducted in this study followed the same procedures as those outlined in our previous research methods.[35] We adhered to the same stringent protocols for EEG preprocessing, and analysis.

Resting-state EEG was carried out using the 10–20 system with 19 electrodes and a digital electroencephalograph (Comet AS40 amplifier EEG GRASS; Telefactor USA). Electrode skin impedance was kept below 5 kΩ. The EEG signal, filtered with a bandpass of 0.5–70 Hz, was digitized and stored for further analysis. Sampling involved over 15 minutes of alternating eyes-open and eyes-closed periods at a rate of 200 Hz. During recording, patients were in a sound-attenuated room in a resting position. Noise preprocessing and group analyses were conducted using iSyncBrain®, v.1.0 (iMediSync Inc., Republic of Korea), an AI-powered cloud-based platform for EEG analysis.

Eyes-closed EEG segments were uploaded to iSyncBrain® for automatic preprocessing to generate cleaned EEG data. Detailed preprocessing involved bandpass filtering in the range of 1~45.5Hz, application of a notch filter at 60Hz to remove power supply noise, common average reference application to eliminate globally mixed noise, and removal of artifact components through bad epoch rejection and adaptive mixture independent component analysis (amICA).

Power spectral density (PSD) analysis was computed using Fast Fourier Transform (FFT) with Hamming window to minimize spectral leakage. Relative power was calculated for each frequency band by dividing the absolute power in each band by the total power across all frequency bands (1–45 Hz), expressed as a percentage. Relative power at eight frequency bands (delta [1–3.99 Hz], theta [4–7.99 Hz], alpha1 [8–9.99 Hz], alpha2 [10–11.99 Hz], beta1 [12–14.99 Hz], beta2 [15–19.99 Hz], beta3 [20–29.99 Hz] and gamma [30–44.99 Hz]) was calculated using power spectrum analysis.

Relative Power Calculation

$$\text{Relative Power } (\%) = (\text{Absolute Power in Band}/\text{Total Power}) \times 100$$

Where:

$$\text{Total Power} = \Sigma(\text{Power from } 1 - 45\text{Hz})$$

Power Spectral Density

$$PSD(f)=|X(f)|\ /(fs\times\ N)$$

Where:

X(f) = FFT of the signal
fs = sampling frequency
N = number of samples

Frequency Band Ratios

$$\text{Theta/Beta Ratio(TBR)} = \text{Power}(4-7.99\text{Hz})/\text{Power}(12-29.99\text{Hz})$$

$$\text{Theta/Alpha Ratio(TAR)} = \text{Power}(4-7.99\text{Hz})/\text{Power}(8-11.99\text{Hz})$$

$$\text{Delta/Alpha Ratio(DAR)} = \text{Power}(1-3.99\text{Hz})/\text{Power}(8-11.99\text{Hz})$$

Statistical Analysis

All statistical analyses were performed using R version 4.1.2. Paired *t*-tests were conducted to evaluate pre- and post-intervention differences within each group (intervention and control). To account for multiple comparisons across the 19 EEG channels, the Bonferroni correction was applied, adjusting the significance threshold to $\alpha = 0.00263$ ($\alpha = 0.05/19$). Results were considered statistically significant if the adjusted p-value was below this threshold (0.05). Descriptive statistics, including means and standard deviations, were reported for all relevant variables.

Results

The EEG analysis reveals distinct changes in power across multiple frequency bands in the intervention and control groups, both visually and statistically.

EEG Power Distribution

Figure 1 illustrates the changes in electroencephalography (EEG) power distribution across various frequency bands (Delta, Theta, Alpha 1, Alpha 2, Beta 1, Beta 2, Beta 3, and Gamma) before (G1) and after (G2) a two-week course of PBDP treatment. Each row represents a different frequency band, detailing the mean EEG power topographies pre-treatment (G1) and post-treatment (G2), the difference between these conditions (G2-G1), and the statistical significance of observed changes (p-value). The topoplots use color gradients to depict the intensity of EEG activity across the scalp, where warmer colors (eg, red, orange) indicate higher activity, and cooler colors (eg, blue, green) indicate lower activity. The topographic maps show a subtle decrease in Delta EEG power specifically in the C3 and Pz areas post-treatment. For the Theta band, the topographic map reveals a decrease in power in the Cz area following treatment. These reductions align with findings reported in the supplementary table. Alpha bands (1 and 2) power increases were observed particularly in the central and occipital regions compared to pre-treatment conditions. Some of these changes are statistically significant. Post-treatment Beta band (1, 2, and 3) powers were evidently increase, particularly in Beta 1 and Beta 3 bands, with several areas showing significant changes. Gamma Band were also increased activity post-treatment in specific regions with some changes reaching statistical significance.

Figure 2 presents topographic maps depicting changes in EEG power across various frequency bands in a control group without therapeutic intervention. The Delta band power showed incremental changes in C4 and some other areas from baseline to follow-up. There was a visible increase in Theta power at the central region (Cz) from baseline to follow-up, as highlighted in the difference map, but this change was not statistically significant. Both Alpha bands show minimal changes between the two time points. Alpha 1 was minimal decrease in frontal but Alpha 1 and 2 were relatively uniform with few significant changes, suggesting that Alpha activity remains stable over time in the control group. The Beta 2 band shows significant increases in parietal regions but global Beta and Gamma band associated no statistically significant changes in p-value map.

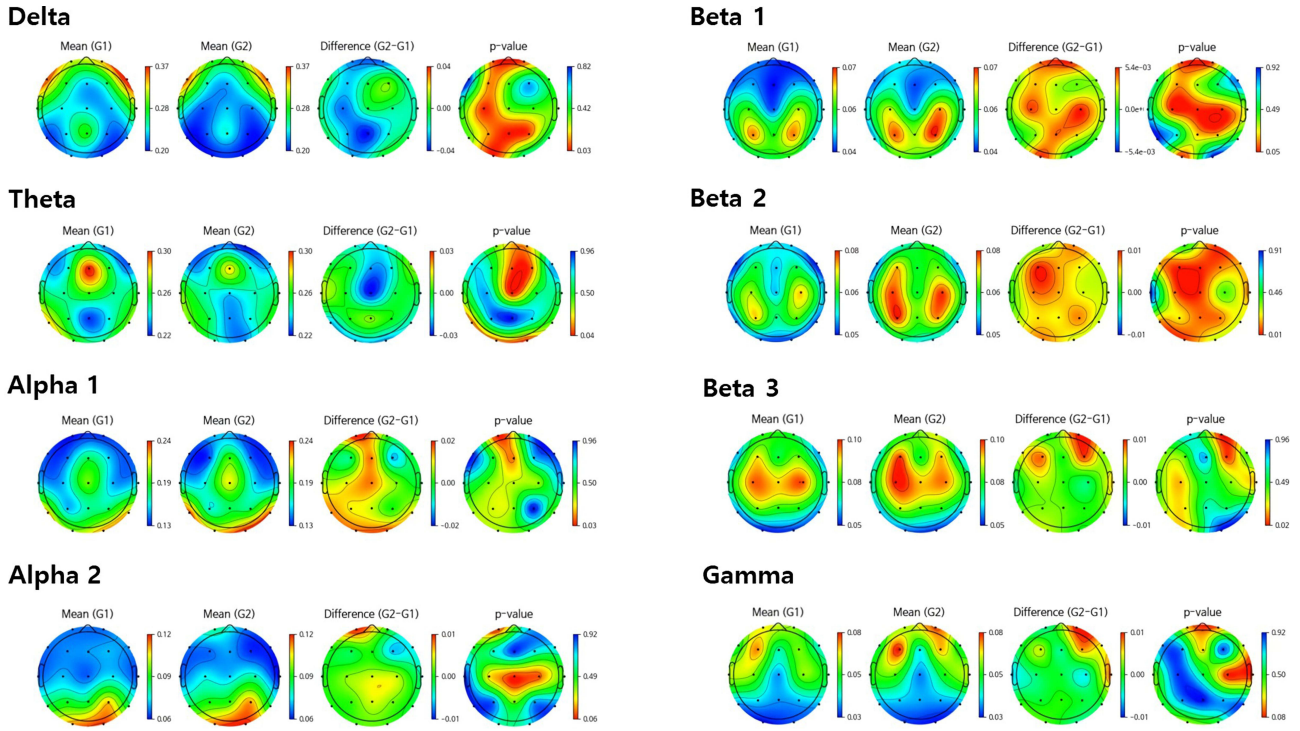

Figure 1 Comparative topographic maps of EEG power distribution before (G1) and after (G2) a two-week course of Porcine Brain-Derived Peptide Mixture (PBDP) injection. These maps represent group-level analyses derived from the averaged EEG power across all participants in the treatment group (n = 27). The maps depict changes in Delta, Theta, Alpha 1, Alpha 2, Beta 1, Beta 2, Beta 3, and Gamma frequency bands. Warmer colors indicate higher EEG activity, while cooler colors indicate lower activity. Statistical significance is denoted on the p-value map.

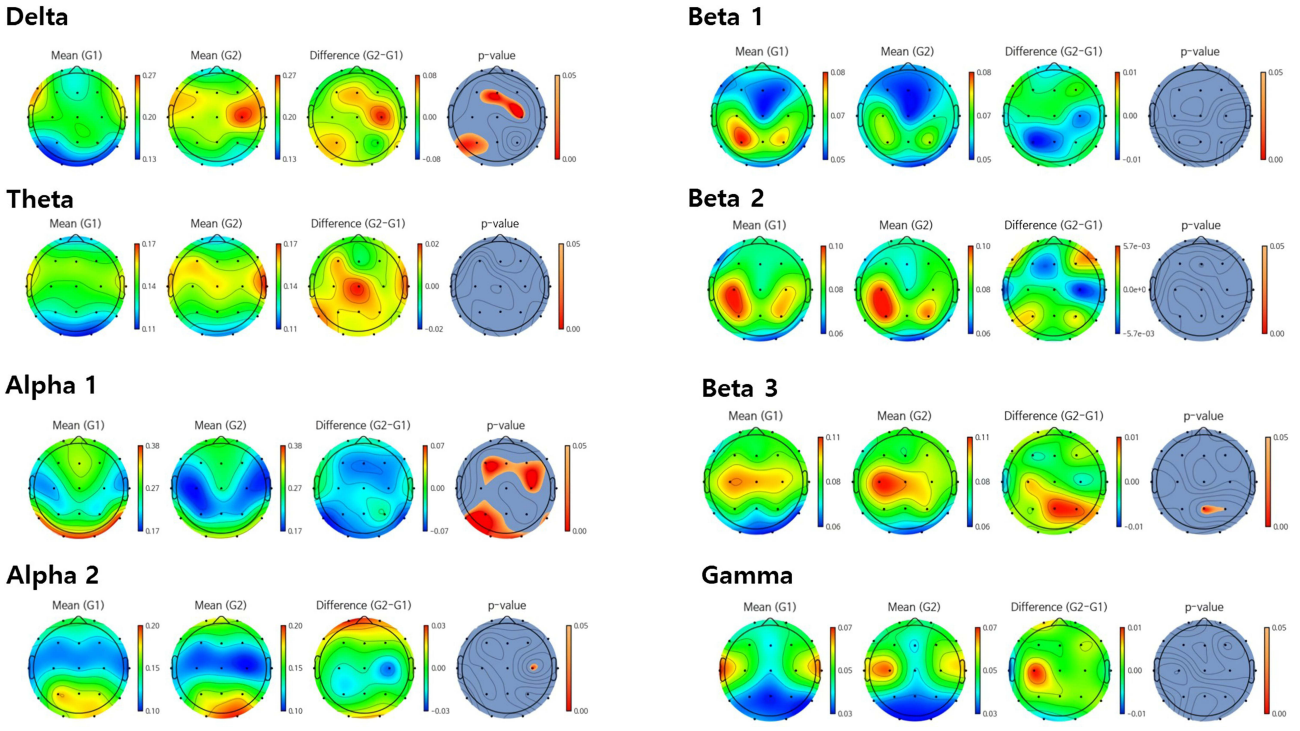

Figure 2 Comparative topographic maps of EEG power distribution baseline (G1) and follow-up (G2) of control group (n = 20). The maps depict changes in Delta, Theta, Alpha 1, Alpha 2, Beta 1, Beta 2, Beta 3, and Gamma frequency bands. Warmer colors indicate higher EEG activity, while cooler colors indicate lower activity. Statistical significance is denoted on the p-value map.

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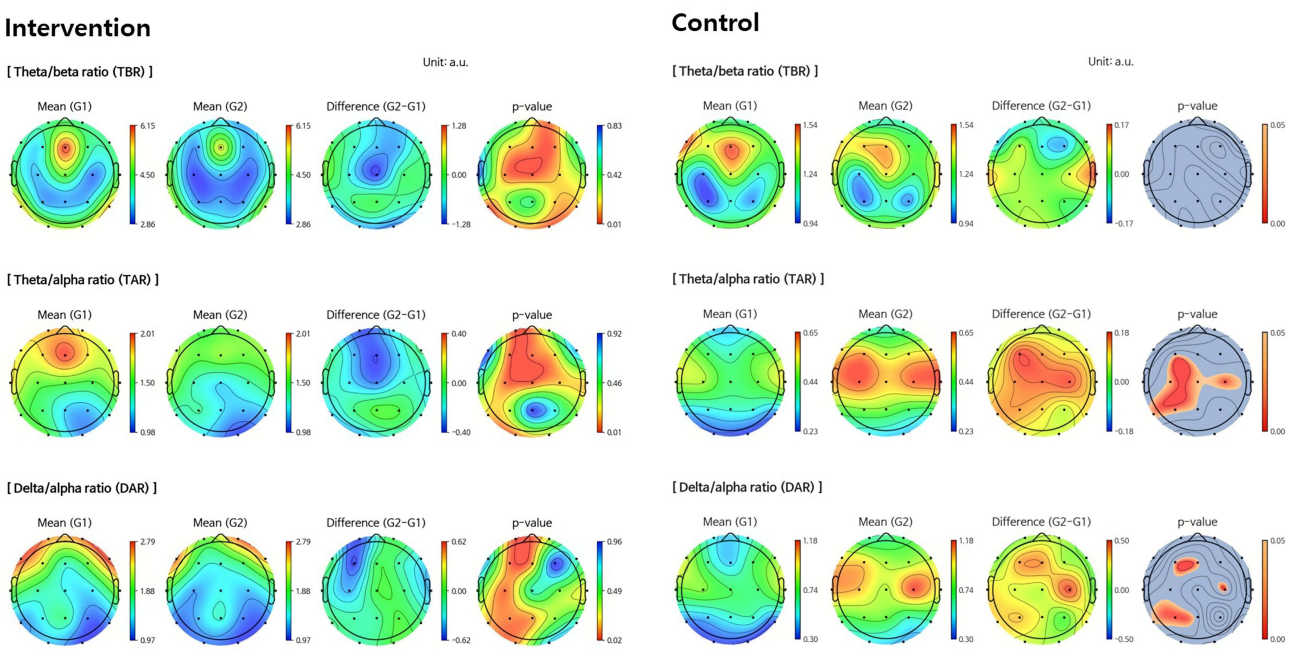

Figure 3 Group-level changes in Theta/Beta Ratio (TBR), Theta/Alpha Ratio (TAR), and Delta/Alpha Ratio (DAR) after a two-week course of Porcine Brain-Derived Peptide Mixture (PBDP) injection. These figures reflect group-averaged EEG power distribution before (G1) and after (G2) for the treatment group (n = 27). Warmer colors indicate higher EEG activity, while cooler colors indicate lower activity. Statistical significance is denoted on the p-value map.

Theta/Beta, Theta/Alpha, and Delta/Alpha Ratios

Figure 3 illustrates the changes in Theta/Beta Ratio (TBR), Theta/Alpha Ratio (TAR), and Delta/Alpha Ratio (DAR) after a two-week course of PBDP injections in the intervention group. In intervention group, notable decreases in TBR and TAR were observed in the central regions, although the p-values suggest that these changes are not universally significant across all regions. And decrease in DAR is observed in left frontal. However, in control group, there were increase in TAR and DAR in the frontal and some scattered areas and the p-value maps show some areas of statistical significance. These findings were analyzed using paired *t*-tests which are appropriate since they satisfy normality conditions required for parametric tests.

Statistical Analysis

In the frontal region of the intervention group, there was a decrease in all three ratios from baseline to follow-up (Table 2). Specifically, TBR decreased from 4.437 ± 3.979 at baseline to 3.859 ± 3.587 at follow-up (p = 0.442). TAR also reduced from 1.815 ± 1.637 to 1.578 ± 1.304 with statistical significance; likewise for DAR which decreased significantly from 2.365 ± 2.471 to 2.105 ± 2.402. Conversely, in the control group's frontal region, changes of TBR and TAR were not significant.

Table 2 TBR(θ/ß), TAR(θ/α) and DAR(δ/α) Ratio Changes After PBDP Treatment for 2 Weeks

Condition		Intervention (n = 27)			Control (n = 20)		
		Baseline	Follow-Up	p-value	Baseline	Follow-Up	p-value
Frontal	TBR	4.437 ± 3.979	3.859 ± 3.587	0.442	4.059 ± 1.635	3.918 ± 1.32	0.6259
	TAR	1.815 ± 1.637	1.578 ± 1.304	0.0062	1.218 ± 1.317	2.547 ± 2.493	0.1618
	DAR	2.365 ± 2.471	2.105 ± 2.402	0.0163	1.977 ± 0.439	0.849 ± 0.831	0.1778
Central	TBR	3.749 ± 3.5099	3.071 ± 2.668	0.0461	3.522 ± 1.458	3.672 ± 1.131	0.5087
	TAR	1.519 ± 1.254	1.290 ± 0.916	0.3246	1.372 ± 0.462	1.851 ± 0.822	0.0066
	DAR	1.498 ± 1.618	1.321 ± 1.570	0.3016	2.196 ± 1.599	3.09 ± 1.701	0.0106

(*Continued*)

Table 2 (Continued).

Condition		Intervention (n = 27)			Control (n = 20)		
		Baseline	Follow-Up	p-value	Baseline	Follow-Up	p-value
Temporal	TBR	5.110 ± 4.861	4.770 ± 5.029	0.5165	3.927 ± 1.713	4.143 ± 1.815	0.4933
	TAR	1.589 ± 1.337	1.416 ± 1.099	0.9234	1.224 ± 0.447	1.53 ± 0.834	0.0408
	DAR	1.600 ± 1.643	1.411 ± 1.453	0.7916	1.802 ± 1.185	2.466 ± 2.013	0.0277
Parietal	TBR	3.428 ± 3.486	3.252 ± 3.461	0.1785	3.067 ± 1.179	3.141 ± 1.323	0.7721
	TAR	1.261 ± 0.956	1.245 ± 0.977	0.0345	1.059 ± 0.378	1.376 ± 0.774	0.0628
	DAR	1.413 ± 1.478	1.310 ± 1.831	0.075	1.611 ± 1.086	2.187 ± 1.521	0.0776
Occipital	TBR	5.146 ± 5.472	4.164 ± 4.633	0.0837	3.827 ± 1.614	3.966 ± 1.539	0.6414
	TAR	1.303 ± 1.224	1.009 ± 0.990	0.0436	0.72 ± 0.453	0.963 ± 0.927	0.2152
	DAR	1.137 ± 1.212	1.051 ± 1.256	0.1241	0.921 ± 0.954	1.428 ± 1.635	0.1585
MDS-OAß		1.073 ± 0.046	1.041 ± 0.028	0.4037			

Note: Paired *t*-test: This parametric test satisfied the assumption of normality.
Abbreviations: PBDP, porcine brain-derived peptide mixture; TBR, theta/beta ratio; TAR, theta/alpha ratio; DAR, delta/alpha ratio; MDS-OAß, multimer detection system-oligomeric amyloid-β.

In the PBDP treatment group, there was a decrease in the power of slow wave bands and an increase in fast wave bands. These changes were statistically significant in the frontal, central, parietal, and occipital areas. On the contrary, in control group, an increase in slow wave band power and a decrease in fast wave band power were significant in the central temporal area. This trend was generally observed across all measurements. The relative power at each sensor level has been provided in the supplementary table, which is included as part of the study's results.

Discussion

This study focused on patients registered in the dementia registry who clinically presented with early-stage AD dementia. The drug administered in this study, PBDP, was approved for regular treatment in patients with AD.[36] Out of the registered registry, we reviewed records of 27 AD patients who received injections of PBDP and underwent electroencephalograms at two-week intervals, along with a control group of 20 AD individuals who received no additional treatment beyond their existing medications. Both the PBDP treatment group and control group consisted of AD patients who were maintaining their basic AD treatments including donepezil stably prior to and during the study.

As previously established, in degenerative brain diseases such as AD, the power band of fast waves (alpha or beta band) on EEGs decreases compared to healthy individuals, while the power band of slow waves (delta or theta band) increases.[21,37,38] Therefore, functional improvement in degenerative brain diseases can be predicted by an increase in the power band of fast EEG waves and a decrease in the power band of slow EEG waves.[25,27–29] Our study also showed significant improvements in quantitative EEG (qEEG) patterns reflecting brain function after just two weeks of PBDP treatment in AD patients. The qEEG analysis from the supplementary Table 1 showed significant decreases across multiple frequency bands when comparing baseline to post-treatment measurements in the PBDP intervention group, particularly in slow wave delta and theta activities (supplementary Table 1). The control group exhibited minimal changes between assessments. Reductions were noted in delta/alpha, theta/alpha, and theta/beta ratios in frontal, central, parietal and occipital regions in the PBDP group (Table 2). The reductions in qEEG ratios observed in this study, such as delta or theta, are suggestive of improving cognitive function.[39,40] However, the clinical significance of these changes requires further context. Future research should aim to establish clear relation of clinical findings and qEEG metrics.

We applied the Bonferroni correction to account for multiple comparisons across the 19 EEG channels analyzed. The significance threshold was adjusted to $\alpha = 0.00263$ ($\alpha = 0.05/19$). After applying this correction, we identified a statistically significant decrease in Alpha 1 band power at the T5 and P3 channels in the control group. No other

channels showed significant changes following the correction. These results emphasize that while localized changes were detected, broader patterns did not reach statistical significance after controlling for multiple comparisons.

Additional statistical analyses were performed to compare EEG power metrics between the intervention and control groups at baseline and follow-up (supplementary Table 2). At baseline, significant differences were observed between the groups in δ and θ power (higher in the intervention group, $p < 0.001$) and α1 and α2 power (higher in the control group, $p < 0.001$). No significant differences were found in ß1, ß3, and γ power, while ß2 showed marginal significance ($p = 0.033$). Post-intervention, δ and θ power remained significantly higher in the intervention group ($p < 0.001$), and α1 and α2 power continued to be significantly higher in the control group ($p < 0.001$ and $p = 0.007$, respectively). No significant differences were observed for ß1, ß3, or γ power at follow-up, and ß2 retained marginal significance ($p = 0.021$). These results indicate that while within-group changes were evident in the intervention group, the between-group comparisons did not demonstrate significant differences in EEG metrics at follow-up.

Baseline analyses revealed significant differences in δ, θ, α1, and α2 power between the intervention and control groups, which may have influenced the observed outcomes. While within-group improvements in δ, θ, and α power were noted in the intervention group, these changes did not result in significant differences between the groups at follow-up. This highlights a limitation of the study, as stronger between-group differences in favor of the intervention group would have provided more robust evidence of the efficacy of PBDP. Future studies should prioritize baseline matching of EEG metrics and incorporate an active placebo group to better account for potential confounding factors and placebo effects.

In clinical trials assessing drug efficacy, determining treatment effects typically requires long timeframes and substantial costs. However, utilizing electrophysiological biomarkers such as qEEG could enable more rapid detection of potential therapeutic benefits, thereby improving efficiency in terms of time and cost.[28,29]

Although not included as objectives of this study, we conducted supplemental caregiver interviews two weeks after the PBDP injection therapy to gather subjective impressions on changes in memory, language, mood, behavior and daily activities (supplementary figure). However, only 18 caregivers of the 27 patients who received PBDP intervention therapy responded using the following 1–100 scale. A baseline score of 100 was set, with improvements or declines indicated in the 0–200 range compared to baseline. Out of the 18 patients whose caregivers responded, 8 showed improvements in memory, 5 in language skills, 10 in mood, 6 in abnormal behavior, and 10 in daily living activities. The areas with the most frequently noted improvements were mood and daily living. One patient showed large improvements across all five categories. Four patients showed no changes in any parameter. In summary, over 50% of PBDP-treated patients with AD exhibited improvements in mood, while around 30–45% showed gains in memory, language, behavior and daily living skills based on caregiver perceptions. Caregiver-reported improvements in patient behavior and cognition, while valuable, are inherently subjective and may be influenced by placebo effects. Research indicates that caregivers often perceive improvements when patients participate in experimental treatments, irrespective of the actual efficacy of the intervention.[41] In this study, the absence of an active placebo group limits our ability to definitively exclude placebo effects as a contributing factor to the observed improvements in the intervention group. Future studies should incorporate an active placebo group to better control for these effects and provide a more robust assessment of treatment efficacy.

Additionally, the lack of demonstrated correlations between caregiver-reported outcomes and observed qEEG changes further limits the interpretation of the findings. While reductions in specific qEEG ratios, such as delta/theta, have been described as suggestive of positive effect on cognition, future research should aim to directly link these objective qEEG metrics with subjective caregiver-reported outcomes.

While neuropsychological assessments could have been utilized as a clinical endpoint to evaluate changes after treatment, the short 2-week timeframe of this study approaches the limits of repeat neuropsychological testing due to practice effects. Many pharmacological trials employ cognitive batteries as outcome measures but test at longer intervals of 3–6 months to minimize learning on repeat exposure. However, completely eliminating practice effects remains a challenge, especially in early-stage AD, mild cognitive impairment, and subjective cognitive decline populations. Consequently, detecting subtle cognitive changes on a neuropsychological exam after only 2 weeks of an investigational treatment like PBDP poses difficulties. Therefore, brief caregiver interviews were conducted to capture any noticeable changes perceived after the 2-week PBDP treatment course. The qEEG changes aligned with this caregiver-reported improvements in memory, language,

mood and daily activities in over 50% of PBDP-treated patients. The qEEG metrics may objectively validate the subjective perceptions of cognitive and functional gains following brief PBDP administration.

Furthermore, we measured the oligomerization tendency of amyloid beta in the blood of the PBDP treated patients using Multimer Detection System-Oligomeric Amyloid-β (MDS-OAβ). This is a diagnostic tool used to measure the risk of possessing AD pathology. Fifteen patients showed decreased MDS-OAß scores indicating reduction of amyloid oligomerization after PBDP treatment, while 12 patients had score increases. A paired *t*-test was conducted to compare the scores before and after PBDP treatment. There was a slight decrease in them from 1.045 ± 0.255 (mean ± SD) at baseline to 1.041 ± 0.168 (mean ± SD) at the 2 week follow up after PBDP treatment; however, this difference was not statistically significant ($t(26) = 0.123$, $p = 0.903$). This may be because, while the drug improves functional aspects, it might not have a role in modifying beta-amyloid pathology associated with AD. Additional studies with larger sample sizes and longer durations are warranted to further investigate the preliminary trend toward decreased oligomerization after PBDP administration.

This study utilized clinical EEG data collected from hospital records, where a high-pass filter at 1 Hz was applied as per standard hospital protocol. While this approach allowed for consistent data acquisition, it may have introduced limitations in the analysis of delta-band activity (1–3.99 Hz) due to the proximity of the filter cutoff to the frequency range of interest. Such filtering choices can potentially attenuate low-frequency signals and induce artifacts, which might influence the accuracy of delta-band measurements. Best practices recommend the use of a high-pass filter with a cutoff much lower than the lowest frequency of interest (eg, 0.1 Hz) to preserve signal integrity. Additionally, a high-pass filter at 0.5 Hz is commonly advised for minimizing artifacts in delta-band studies. Recognizing this limitation, future research will aim to implement optimal filtering protocols that adhere to these recommendations, ensuring enhanced signal quality and data reliability.

This study provides promising insights into the potential therapeutic effects of PBDP in treating AD, particularly focusing on improvements in quantitative EEG patterns in AD patients after treatment. We observed significant reductions in Theta/Beta, Theta/Alpha, and Delta/Alpha ratios across brain regions, suggesting enhanced cortical activity and possible cognitive improvements. Interestingly, while qEEG metrics showed functional enhancements, there were no significant changes in amyloid-beta oligomerization, indicating PBDP may improve brain function without directly influencing AD amyloid pathology. This dissociation suggests a complex mechanism of action likely mediated by neurotrophic factors that support neuronal health and plasticity independent of amyloid dynamics. Moreover, subjective caregiver interviews reported memory, language, mood, and daily living improvements in over 50% of PBDP-treated patients. Further research with more patients over longer periods is necessary to validate these preliminary findings on the therapeutic potential and mechanisms of PBDP for AD. Additionally, more advanced biomarkers and neuroimaging could elucidate the broader impacts of PBDP on brain structure/function in AD.

Conclusion

This exploratory study provides preliminary evidence for the therapeutic potential of PBDP in AD patients through qEEG analysis. PBDP treatment demonstrated significant electrophysiological improvements in AD patients, with reductions in pathological EEG ratios (Theta/Alpha, Delta/Alpha) and increases in beneficial frequency bands (alpha, beta) at 2-month follow-up. Over 50% of patients showed caregiver-reported improvements in mood and daily activities.

However, several limitations must be acknowledged. The retrospective design, small sample size (n = 27 intervention, n = 20 control), absence of placebo control, and baseline EEG differences between groups limit the generalizability of our findings. Additionally, the lack of direct correlation between qEEG changes and standardized cognitive assessments represents a significant limitation.

Despite these limitations, our findings suggest that qEEG may serve as a sensitive biomarker for monitoring acute therapeutic responses in AD treatment, potentially enabling more efficient evaluation of novel interventions. PBDP demonstrates promise as a potential adjunctive therapy for AD management, though larger prospective, randomized, placebo-controlled trials with standardized cognitive outcomes are essential to establish definitive clinical efficacy and determine optimal treatment protocols.

Abbreviations

AD, Alzheimer's disease; BDNF, brain-derived neurotrophic factor; CNTF, ciliary neurotrophic factor; DAR, Delta/Alpha Ratio; GDNF, glial cell line-derived neurotrophic factor; MDS-OAβ, multimer detection system-oligomeric amyloid-β; NGF, nerve growth factor; PBDP, porcine brain-derived peptide mixture; qEEG, quantitative electroencephalography; TAR, Theta/Alpha Ratio; TBR, Theta/Beta Ratio.

Data Sharing Statement

The datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request. Please contact "Youn YC" (e-mail: neudoc@cau.ac.kr) for data access inquiries.

Ethical Approval

This study was retrospectively conducted on patients registered in the CAU dementia registry (IRB registration No. 2009-005-19331). This study was conducted in accordance with the ethical standards based on a protocol reviewed by the Institutional Review Board (IRB) (No 2311-001-19495), which was conducted in accordance with the Declaration of Helsinki.

Consent to Participate

This study was conducted retrospectively using de-identified data from participants registered in the CAU dementia registry. As such, obtaining individual consent was not applicable and informed consent was waived. The study protocol was reviewed and approved by the Institutional Review Board (IRB registration No. 2311-001-19495).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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