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ORIGINAL PAPER

Clinical Implications of Quantitative Electroencephalography and Current Source Density in Patients with Alzheimer's Disease

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Abstract This study examined whether quantitative electroencephalography (qEEG) and current source density (CSD) can be used to evaluate symptom severity in Alzheimer's disease (AD) patients. Thirty AD patients (13 mild and 17 moderate severity) and 30 normal control (NC) subjects were recruited. The Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet and the Global Deterioration Scale were measured. qEEG and CSD data were analyzed in five frequency bands: delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–25 Hz), and gamma (30–50 Hz). Compared with the NC subjects, the moderate AD patients had significantly increased theta and decreased beta power. Compared with the mild AD patients, the moderate AD patients had significantly decreased beta power. In the AD patients, the theta power was significantly correlated with a poor performance for global cognition; however, beta power was positively correlated with a good performance for global cognition, attention, memory, visuospatial function, and executive function. The CSD of the theta band in the superior temporal gyrus, transverse temporal gyrus, insula, postcentral gyrus, cuneus, and lingual gyrus was significantly different between NC subjects and moderate AD patients and between mild and moderate AD patients. The theta CSD of these regions was significantly correlated with a poor performance for global cognition, memory, visuospatial function, execution, and language. The results suggest that qEEG and the CSD of the theta and beta bands are useful biological markers in AD patients.

Keywords Alzheimer's disease · qEEG · Current source density · Biological marker · Symptom severity

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Introduction

Dementia is a neurodegenerative disorder that affects a person's mental capacities and cognitive functions. The most common form of dementia among the elderly population is Alzheimer's disease (AD), which accounts for 50–60 % of all causes of dementia. The possibility of developing AD doubles approximately every 5 years after 65 years of age. After 85 years of age, the risk reaches nearly 50 % (Brookmeyer et al. 1998; Jorm and Jolley 1998).

The biological markers of AD are not yet fully determined, and the diagnosis of dementia is still dependent on clinical assessments and neuropsychological examinations. Electroencephalography (EEG) and quantitative EEG (qEEG) are considered to be useful diagnostic tools for AD because they are believed to reflect cerebral functions with a high temporal resolution (Fogelson et al. 2003; Jelic and Kowalski 2009; Knott et al. 2001). Previous studies using

EEG and qEEG have revealed that AD patients demonstrate a significant association with increased slow waves (theta and delta bands) and decreased fast waves (alpha and beta bands) as compared to normal elderly subjects (Bennys et al. 2001; Jung et al. 2007; Prichep 2007; Maurer and Dierks 1992; Schreiter-Gasser et al. 2008; Lee et al. 2010; Park et al. 2008). It is of clinical interest to find the relationship between these EEG abnormalities and the cognitive deficits that characterize AD. Knott et al. (2001) reported that there was a correlation between the scores of the Mini-Mental Status Examination (MMSE), which reflect global cognitive functions, and qEEG. The delta and theta power bands were negatively correlated with MMSE scores, while the alpha and beta power bands were positively correlated with MMSE scores. Additionally, Gianotti et al. (2007) reported that cortical delta waves showed a negative correlation with MMSE scores, while alpha waves showed a positive correlation.

Furthermore, standardized low-resolution brain electromagnetic tomography (sLORETA) was recently introduced (Pascual-Marqui 2002), which can identify the current source density (CSD) of various cortical level qEEG or event related potential components based on the Montreal Neurological Institute (MNI) 152 template (Fuchs et al. 2002). This technique can also identify CSD differences between two groups for their corresponding Brodmann areas (BAs) or cerebral gyri, thereby allowing reliable spatial and temporal detection of brain cortical activity (Pascual-Marqui 2002). By using this analysis, the source activity of EEG or qEEG responses can be detected and evaluated for various psychiatric illnesses. AD patients showed a decreased CSD of the alpha band in the right temporal lobe and right inferior parietal lobule compared with healthy controls (Sherlin et al. 2006); however, the CSD of the delta and theta bands was increased in the right temporal lobe and cingulate gyrus in AD patients (Sherlin 2009). Gianotti et al. (2007) reported that AD patients showed increased CSD of the delta and theta frequency bands, mainly in the left temporo-parieto-occipital area, compared to healthy controls; meanwhile, decreased CSD of the high alpha and beta frequency bands was observed in the temporo-parieto-occipital area. They also reported a significant negative correlation between the MMSE scores and the CSD of the delta frequency band in the left parietal area and a significant positive correlation between the MMSE scores and the CSD of the low alpha band in the left temporal area. Babiloni et al. (2004) reported that the CSD of the central, parietal, temporal, and limbic low alpha bands, which was specific to a mild AD patient group, was reduced compared to healthy controls and vascular dementia patients. The CSD of the delta bands in the occipital or temporal areas in patients with mild cognitive impairment (MCI) and AD showed a significant negative correlation with the corsi span forward score, while the CSD of the low alpha bands in the occipital area showed a negative correlation with the digit span forward score (Babiloni et al. 2007).

However, most of the previous studies used only a few neuropsychological screening tools, such as the MMSE, which are not sufficient to provide information about the functional capacity of extensive neuropsychological functions in AD patients. In addition, previous studies used 19-channel EEG, which is not sufficient to analyze source activity (Michel et al. 2004). Thus, more comprehensive assessment tools, including various domains of cognitive function, and 64-channel EEG measurements are necessary to enhance our understanding of the relationship between qEEG and neuropsychological function in AD patients.

The Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet (CERAD-K) is considered a reliable and valid assessment procedure for AD (Lee et al. 2002). CERAD-K appears to be an effective tool to detect dementia and MCI. Using CERAD-K, Kim et al. (2011a) successfully studied the prevalence of dementia and MCI and the factors associated with the risk of dementia in a representative nationwide sample of Korean elders aged 65 years or older. The present study used CERAD-K to investigate comprehensively the cognitive dysfunctions associated with AD patients.

In this study, we used CERAD-K and 64-channel EEG. We examined the differences in qEEG and CSD between AD patients and healthy elderly subjects, and also explored the relationships between these two EEG variables (qEEG and CSD) and CERAD-K scores. We hypothesized that: (1) AD patients would show increased slow wave activity and decreased fast wave activity compared to healthy elderly subjects, and (2) the qEEG and CSD, when AD patients and healthy controls show significant differences, would be significantly correlated with the neuropsychological test scores in the AD group.

Materials and Methods

Subjects

Thirty patients with AD (mean age = 76.57 ± 5.63 years) and 30 healthy controls (NC; mean age = 75.27 ± 5.81 years) were recruited from the Psychiatry Department of Inje University Ilsan Paik Hospital, Korea. AD patients were diagnosed by structured diagnostic evaluation using CERAD-K (Lee et al. 2002). Those who showed other medical conditions known to cause dementia—determined by neurological, serological, and imaging tests including computed topography and magnetic resonance imaging—

were excluded from this study. The severity of AD was determined according to the Global Deterioration Scale (GDS; Reisberg et al. 1982): mild severity (GDS 3–4) and moderate severity (GDS 5–6).

The age-, sex-, and education level-matched 30 NC subjects were recruited from social communities around the hospital through posters and local newspapers. They were examined by a trained psychiatrist according to the CERAD-K protocol. In Korea, NC subjects could have low MMSE scores due to their low educational levels (Kim et al. 2011b); however, their relatively intact cognitive functions were confirmed with CERAD-K. They had no personal history of psychiatric or neurological abnormalities. Reliable informants were also interviewed to acquire additional information regarding the cognitive and functional capacity and medical history of the subjects. All subjects provided written informed consent prior to their participation in this study. This study was approved by the Institutional Review Board of Inje University Ilsan Paik Hospital.

Neuropsychological Tests

CERAD-K consisted of a standardized clinical interview on demographic information, cognitive and functional capacity, drug inventory, depression and medical history, a cognitive state examination, and a general physical and neurological examination (Lee et al. 2002). CERAD-K compares the test scores of subjects with the predetermined norm of cognitively healthy Korean elderly individuals. The norm was developed based on the sex, education, and age differences in the Korean population.

The CERAD-K includes the following 11 tests: (1) the MMSE in CERAD-K (MMSE-KC), (2) the Korean version of the short blessed test (SBT-K), (3) word list memory (learning a visually presented list of ten words, three trials), (4) word list recall (delayed word list recall), (5) word list recognition (recognition of previously studied words among non-studied words), (6) the Korean version of the Boston naming test (K-BNT; naming of line drawings), (7) word fluency (animal category verbal fluency), (8) constructional praxis (copying figures), (9) constructional recall (delayed figure recall), and (10) trail making test A and (11) trail making test B (TMT A and B, respectively; timed connection of a labeled circle).

The SBT-K (Lee et al. 1999) measures orientation, memory, and concentration. It consists of six shortened items that ask subjects to identify the year, month, and time, to count backwards from 20 to 1, to say weekdays and seasons in reverse order, and to recall their names and addresses. The SBT-K score ranges from 0 (no errors) to 28 (maximum errors). In TMT A, subjects are asked to draw lines sequentially connecting 25 encircled numbers distributed on a sheet of paper. In TMT B, subjects are instructed to draw lines alternating between numbers and Korean letters (e.g., (1) 가, (2) 나, (3) 다, etc.). In TMT A and B, the scores are based on how long it takes to complete the task. Thus, lower scores in the SBT-K, TMT A, and TMT B indicate better performance.

These tests allow us to examine the functional capacity of patients in several cognitive domains: (1) global cognition (MMSE-KC and SBT-K) and attention (TMT A), (2) memory (word list memory, word list recall, word list recognition, and constructional recall), (3) language (K-BNT), (4) visuospatial function (constructional praxis), and (5) executive function (TMT B and word fluency).

EEG Recording and qEEG Analysis

The subjects were seated in a comfortable chair in a sound-attenuated room. The resting EEG was taken with subjects eyes closed for 3 min. The EEG was recorded using a 64-channel quick-cap (Neuroscan), in which 62 scalp electrodes (FP1, FPZ, FP2, AF3, AF4, F7, F5, F3, F1, FZ, F2, F4, F6, F8, FT7, FC5, FC3, FC1, FCZ, FC2, FC4, FC6, FT8, T7, C5, C3, C1, CZ, C2, C4, C6, T8, TP7, CP5, CP3, CP1, CPZ, CP2, CP4, CP6, TP8, P7, P5, P3, P1, PZ, P2, P4, P6, P8, PO7, PO5, PO3, POZ, PO4, PO6, PO8, CB1, O1, OZ, O2, and CB2) were positioned according to the international 10–20 system with a Neuroscan SynAmp amplifier (Compumedics USA, El Paso, TX, USA). A vertical electrooculogram (EOG) was recorded using two electrodes, one located above and one below the right eye. A horizontal EOG was recorded at the outer canthus of each eye. EEG data were recorded with a 0.1–100-Hz band-pass filter at a sampling rate of 1,000 Hz. The ground electrode was placed on the forehead and the reference electrodes were at M1 and M2. EEG data were initially processed using Scan 4.3. Eye movements and blink artifacts were visually screened and rejected by one expert EEG operator. We analyzed the resting EEG data from the eyes closed condition in this study. EEG data were grouped into epochs with a length of ~2 s (2,048 points). Epochs with signals exceeding ± 70 μV on any channel were rejected from the analysis. A total of 15 epochs (~30 s) were prepared for each subject. Fast Fourier transformation was performed on 62 electrode channels into five frequency bands: delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–25 Hz), and gamma (30–50 Hz). A total of six regions were selected for further analysis (Fig. 1): left frontal (AF3, F3, and F5), right frontal (AF4, F4, and F6), left central (C3, C5, and CP3), right central (C4, C6, and CP4), left parieto-occipital (P5, P7, and PO7), and right parieto-occipital (P6, P8, and PO8). These regions were divided based on a previous qEEG study (Zion-Golumbic et al. 2008). The peripheral electrode sites

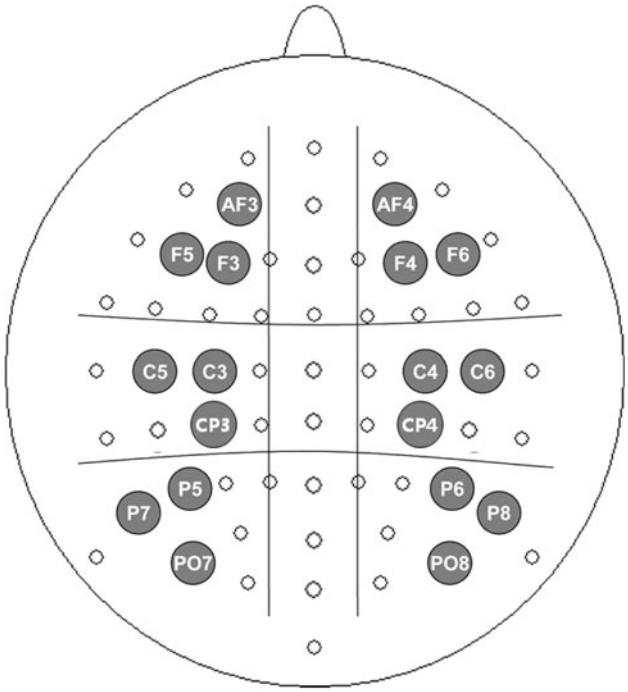

Fig. 1 The 62 EEG recording sites and the demarcation of the six qEEG regions

were not selected, because they could be vulnerable to artifacts. The relative power of three electrodes was averaged in each of these six regions. The relative global band powers were calculated over 62 electrode channels and then averaged (Gianotti et al. 2007; Jung et al. 2007).

To analyze asymmetry, we used the lateral asymmetry index (LAI; Jung et al. 2007). The LAI was determined by comparing the corresponding frequency band percentages for the left and right hemispheres. The LAI was computed by dividing the differences between the two hemispheres by their sum, i.e., $A = (P_{left} - P_{right})/(P_{left} + P_{right})$, where P_{left} and P_{right} are the relative powers of the corresponding frequency band in the appropriate brain region. The resulting values range from 1, when the right hemisphere has zero activity to −1, when the left hemisphere has zero activity. An index of zero indicated equivalent activity in both the hemispheres. A positive LAI points to dominant brain activity in the left hemisphere, whereas a negative LAI indicates dominant brain activity in the right hemisphere.

Analysis of CSD Using sLORETA

CSD of the qEEG band power was calculated using sLORETA (Pascual-Marqui 2002), which analyses the 62-channel EEG signals. sLORETA estimates the standardized CSD using a realistic three-shell head model based on the MNI 152 template provided by the Brain Imaging Center of the MNI (Fuchs et al. 2002). sLORETA was developed on the assumption that the activity of any single neuron should be highly synchronized to the activity of its closest neighbors. The solution space is restricted to the cortical gray matter and hippocampus of the head model and partitioned into 6,239 voxels at a spatial resolution of 5 mm (Pascual-Marqui et al. 1999). Anatomical labels, such as BA, are provided by using an appropriate transformation from MNI to Talairach space (Brett et al. 2002).

Statistical Analysis

Group comparisons of demographic data were performed using the χ^2 test or one-way analysis of the variance (ANOVA) ($p < 0.05$). For the CERAD-K test scores and qEEG relative amplitude, one-way ANOVA was used to assess differences among the three groups. Post hoc analysis was performed using Fisher's least significant difference (LSD) method. Spearman's correlation analysis was performed to evaluate the correlation between qEEG and CERAD-K test scores and between CSD and CERAD-K test scores in the AD patients.

The source activation of the qEEG bands was calculated for each subject using a statistical nonparametric mapping method that was provided by the sLORETA toolbox. This toolbox provides voxel-by-voxel independent t testing to compare groups. The statistical significance is assessed nonparametrically with a randomization test ($n = 5{,}000$) that corrects for multiple comparisons.

Results

Demographic and Clinical Characteristics

The AD group consisted of 30 subjects (22 females and 8 males), and the NC group consisted of 30 subjects (26 females and 4 males). The AD group was comprised of 17 patients with mild AD (mean age = 75.31 ± 5.83 years), and 13 patients with moderate AD (mean age = 78.08 ± 5.18 years). The education level of the mild and moderate AD patients was 5.71 ± 5.67 and 3.54 ± 4.66 years, respectively. The NC group was aged 75.27 ± 5.81 years and had received 5.73 ± 4.23 years of education. There were no significant differences in the demographic data (age, sex, and education level) among the mild AD patients, moderate AD patients, and NC subjects (Table 1).

The test scores of the CERAD-K (MMSE-KC, SBT-K, TMT A/B, word list memory, word list recall, word list recognition, constructional praxis and recall, K-BNT, and word fluency) are presented in Table 2. Moderate AD showed significantly lower MMSE-KC, word list memory,

Table 1 Descriptive statistics of the demographic data of AD patients and NC subjects

		All AD ($N = 30$)	Mild AD ($N = 17$)	Moderate AD ($N = 13$)	NC ($N = 30$)	p
Sex	Male	8	5	3	4	ns[a]
	Female	22	12	10	26	
Age (years)		76.57 ± 5.63	75.41 ± 5.83	78.08 ± 5.18	75.27 ± 5.81	ns[b]
Education (years)		4.77 ± 5.28	5.71 ± 5.67	3.54 ± 4.66	5.73 ± 4.23	ns[b]

ns not significant

$p < 0.05$

[a] χ^2 test

[b] one-way ANOVA

word list recall, word list recognition, constructional praxis, and K-BNT test scores but higher SBT-K test scores than mild AD. Mild AD showed significantly lower MMSE-KC, word list memory, word list recall, word list recognition, constructional recall, K-BNT, and word fluency test scores but higher SBT-K and TMT A test scores than NC. Moderate AD showed significantly lower MMSE-KC, word list memory, word list recall, word list recognition, constructional praxis, constructional recall, K-BNT, and word fluency test scores but higher SBT-K and TMT A than NC.

qEEG and Its Correlation with Neuropsychological Function

The relative powers of the five frequency bands [delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–25 Hz), and gamma (30–50 Hz)] and their global and regional distribution are presented in Fig. 2 and Table 3. Significant differences were mainly found in the power of the theta and beta bands. Globally, the moderate AD group showed significantly higher power of the theta band compared with the NC subjects (13.07 ± 3.51 vs. 10.51 ± 1.55, respectively, $p < 0.05$) and significantly lower power of the beta band compared with the NC subjects (28.30 ± 6.29 vs. 34.94 ± 4.95, respectively, $p < 0.05$). The mild AD group showed significantly higher power of the beta band compared with the moderate AD group (33.13 ± 5.06 vs. 28.30 ± 6.29, respectively $p < 0.05$).

Regionally, the relative powers of the six regions showed similar findings with the relative global power. In left frontal region, the moderate AD group showed significantly higher power of the theta band than did the NC subjects (13.36 ± 4.39 vs. 11.00 ± 2.17, respectively, $p < 0.05$) and significantly lower power of the beta band than did the NC subjects (28.36 ± 6.42 vs. 35.59 ± 5.54, respectively, $p < 0.05$). The mild AD group showed significantly higher power of the beta band than the moderate

Table 2 Neuropsychological tests of the Korean version of the CERAD-K of AD patients and NC subjects. One-way ANOVA was performed with the post hoc LSD method. Significant differences are indicated with asterisks

	Mild AD ($N = 17$)	Moderate AD ($N = 13$)	NC ($N = 30$)	p
MMSE-KC	19.18 ± 3.57	12.31 ± 4.78	25.90 ± 3.48	0.000[a,b,c]
SBT-K	15.94 ± 8.15	22.92 ± 3.17	5.17 ± 6.22	0.000[a,b,c]
TMT A	236.35 ± 129.36	295.92 ± 101.13	117.20 ± 99.16	0.000[b,c]
TMT B	301.06 ± 19.02	304.62 ± 16.64	247.93 ± 72.813	0.109
Word list memory	10.65 ± 3.33	5.46 ± 3.88	13.57 ± 5.46	0.000[a,b,c]
Word list recall	2.88 ± 1.65	0.85 ± 1.28	5.03 ± 2.59	0.000[a,b,c]
Word list recognition	5.53 ± 2.47	3.08 ± 3.01	7.47 ± 3.21	0.000[a,b,c]
Constructional praxis	7.06 ± 2.35	4.08 ± 2.49	8.47 ± 3.33	0.000[a,c]
Constructional recall	1.88 ± 1.69	0.77 ± 1.30	6.20 ± 3.68	0.000[b,c]
K-BNT	7.94 ± 2.56	4.38 ± 1.80	10.00 ± 3.24	0.000[a,b,c]
Word fluency	7.18 ± 3.81	5.00 ± 3.62	12.70 ± 4.40	0.000[b,c]

SD standard deviation, *MMSE-KC* Mini-Mental State Examination in CERAD-K, *SBT-K* Korean version of the short blessed test, *TMT* trail making test, *K-BNT* Korean version of the Boston naming test

[a] between mild AD and moderate AD

[b] between mild AD and NC

[c] between moderate AD and NC

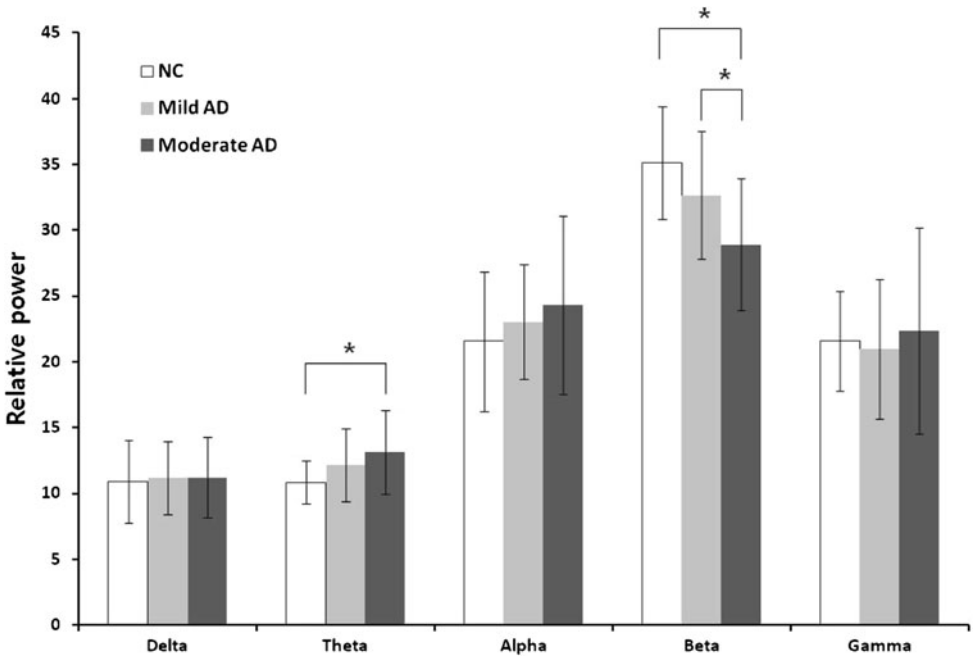

Fig. 2 Relative global power of the delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–25 Hz), and gamma (30–50 Hz) bands in mild to moderate AD patients and NC subjects. The *bars* represent the standard deviation. One-way ANOVA was performed. An *asterisk* indicates a significant difference between the groups after post hoc LSD analysis

AD group did (34.48 ± 5.31 vs. 28.36 ± 6.42, respectively, $p < 0.05$). In the right frontal region, the moderate AD group showed significantly higher power of the theta band than the NC subjects (13.61 ± 4.11 vs. 10.93 ± 2.04, respectively, $p < 0.05$) and significantly lower power of the beta band than the NC subjects did (29.37 ± 6.95 vs. 35.63 ± 5.84, respectively, $p < 0.05$). The mild AD group showed significantly higher power of the beta band than the moderate AD group did (34.69 ± 5.94 vs. 29.37 ± 6.95, respectively, $p < 0.05$).

In the left central region, the moderate AD group showed significantly lower power of the beta band as compared with the NC subjects (28.27 ± 6.64 vs. 37.13 ± 5.81, respectively, $p < 0.05$) and significantly higher power of the gamma band than the NC subjects did (25.51 ± 9.64 vs. 20.55 ± 4.83, respectively, $p < 0.05$). The mild AD group showed significantly higher power of the beta band than the moderate AD group (34.37 ± 5.62 vs. 28.27 ± 6.64, respectively $p < 0.05$) and significantly lower power of the gamma band than the moderate AD group did (19.63 ± 7.04 vs. 25.51 ± 9.46, respectively, $p < 0.05$). In the right central region, the moderate AD group showed significantly higher power of the theta band than the NC subjects (13.68 ± 3.43 vs. 10.21 ± 1.83, respectively, $p < 0.05$) and significantly lower power of the beta band than the NC subjects did (29.48 ± 7.19 vs. 36.56 ± 5.59, respectively, $p < 0.05$). The mild AD group showed significantly lower power of the theta band than the moderate AD group did (11.46 ± 3.15 vs. 13.68 ± 3.43, respectively, $p < 0.05$).

In the left occipital region, the moderate AD group showed significantly higher power of the theta band as compared with the NC subjects (12.55 ± 3.56 vs. 10.36 ± 1.42, respectively, $p < 0.05$) and significantly lower power of the beta band as compared with the NC subjects (28.27 ± 6.14 vs. 34.47 ± 4.88, respectively, $p < 0.05$). The mild AD group showed significantly higher power of the beta band than that of the moderate AD group (32.68 ± 5.24 vs. 28.27 ± 6.14, respectively $p < 0.05$). In the right occipital region, the moderate AD group showed significantly higher power of the theta band than that of the NC subjects (13.11 ± 3.85 vs. 10.21 ± 1.57, respectively, $p < 0.05$) and significantly lower power of the beta band than that of the NC subjects (27.55 ± 6.12 vs. 34.02 ± 5.09, respectively, $p < 0.05$).

However, no significant differences between NC and mild AD were observed.

Table 4 shows the correlation patterns between the qEEG relative power and the CERAD-K test scores in the AD patients. Significant correlations were mainly found in the power of the theta and beta bands. Globally, the power of the theta band showed a significant negative correlation with MMSE-KC ($r = -0.422, p < 0.05$). In addition, the power of the beta band showed significant positive correlations with MMSE-KC ($r = 0.505$, $p < 0.01$), word list memory ($r = 0.408, p < 0.05$), and constructional praxis ($r = 0.454$, $p < 0.05$). Conversely, the power of the beta band showed significant negative correlations with SBT-K ($r = -0.447$, $p < 0.01$) and TMT A ($r = -0.402, p < 0.05$) test scores.

Regional analysis revealed that the power of the beta band showed significant correlations with MMSE-KC, SBT-K, TMT and word list memory test scores in the widespread (particularly central and occipital) cortical regions. And the power of the slow waves (delta and theta) showed significant correlations with MMSE-KC, SBT-K test scores dominantly in right hemispheric region.

Table 3 Relative powers of five qEEG bands in six cortical regions in AD patients and NC subjects. One-way ANOVA was performed with the post hoc LSD method. Significant differences are indicated with asterisks

		Mild AD ($N = 17$)	Moderate AD ($N = 13$)	NC ($N = 30$)	p
Global	Delta	11.18 ± 3.42	11.95 ± 3.64	10.89 ± 2.96	0.621
	Theta	11.80 ± 2.83	13.07 ± 3.51	10.51 ± 1.55	0.009[c]
	Alpha	23.87 ± 6.14	24.75 ± 7.69	22.22 ± 6.49	0.472
	Beta	33.13 ± 5.06	28.30 ± 6.29	34.94 ± 4.95	0.002[a,c]
	Gamma	19.99 ± 6.10	21.91 ± 7.18	21.42 ± 3.97	0.578
Frontal left	Delta	11.35 ± 3.81	12.17 ± 2.79	11.72 ± 4.30	0.849
	Theta	12.32 ± 3.25	13.36 ± 4.39	11.00 ± 2.17	0.063[c]
	Alpha	20.37 ± 5.13	21.72 ± 6.49	19.05 ± 6.42	0.408
	Beta	34.48 ± 5.31	28.36 ± 6.42	35.59 ± 5.54	0.002[a,c]
	Gamma	21.47 ± 7.74	24.37 ± 9.14	22.84 ± 5.90	0.554
Frontal right	Delta	11.29 ± 3.64	11.87 ± 3.17	11.78 ± 4.37	0.899
	Theta	12.70 ± 3.52	13.61 ± 4.11	10.93 ± 2.04	0.021[c]
	Alpha	20.27 ± 5.14	22.92 ± 7.71	18.87 ± 6.21	0.161
	Beta	34.69 ± 5.94	29.37 ± 6.95	35.63 ± 5.84	0.011[a,c]
	Gamma	21.02 ± 7.65	22.21 ± 8.19	22.76 ± 5.32	0.694
Central left	Delta	11.62 ± 4.07	12.86 ± 5.92	11.18 ± 4.06	0.540
	Theta	11.55 ± 2.95	11.94 ± 3.55	10.25 ± 1.69	0.086
	Alpha	22.81 ± 6.25	21.40 ± 6.33	20.86 ± 6.55	0.610
	Beta	34.37 ± 5.62	28.27 ± 6.64	37.13 ± 5.81	0.000[a,c]
	Gamma	19.63 ± 7.04	25.51 ± 9.46	20.55 ± 4.83	0.044[a,c]
Central right	Delta	11.60 ± 4.56	12.61 ± 3.90	10.44 ± 2.96	0.194
	Theta	11.46 ± 3.15	13.68 ± 3.43	10.21 ± 1.83	0.001[a,c]
	Alpha	22.17 ± 6.47	23.60 ± 6.62	21.38 ± 5.84	0.562
	Beta	33.87 ± 6.17	29.48 ± 7.19	36.56 ± 5.59	0.004[c]
	Gamma	20.87 ± 7.51	20.60 ± 6.87	21.38 ± 4.75	0.919
Occipital left	Delta	10.77 ± 3.35	11.33 ± 3.98	10.27 ± 2.97	0.621
	Theta	11.44 ± 3.10	12.55 ± 3.56	10.36 ± 1.42	0.035[c]
	Alpha	28.08 ± 7.68	28.86 ± 10.18	25.44 ± 8.24	0.396
	Beta	32.68 ± 5.24	28.27 ± 6.14	34.47 ± 4.88	0.003[a,c]
	Gamma	17.01 ± 5.41	18.96 ± 7.17	19.43 ± 4.59	0.343
Occipital right	Delta	10.60 ± 3.49	11.24 ± 4.69	9.85 ± 2.27	0.417
	Theta	11.51 ± 2.98	13.11 ± 3.85	10.21 ± 1.57	0.006[c]
	Alpha	27.89 ± 8.47	27.74 ± 9.19	25.58 ± 7.53	0.570
	Beta	31.48 ± 5.18	27.55 ± 6.12	34.02 ± 5.09	0.002[c]
	Gamma	18.50 ± 5.96	20.33 ± 7.99	20.31 ± 4.45	0.552

[a] between mild AD and moderate AD

[b] between mild AD and NC

[c] between moderate AD and NC

CSD and Its Correlation with Neuropsychological Function

CSD showed significant differences between AD patients and NC subjects and between mild AD and moderate AD patients in the theta band. In the other qEEG bands, no significant differences were observed in CSD when they were compared with each of the two groups. CSD of the theta band in the AD group was significantly higher than that of the NC group in the superior temporal gyrus and transverse temporal gyrus ($p < 0.05$, two-tailed; Fig. 3a, Table 5). CSD of the theta band in the moderate AD group was significantly higher than that of the NC subjects in the lingual gyrus, superior temporal gyrus, transverse temporal gyrus, insula, postcentral gyrus, and cuneus ($p < 0.05$, one-tailed; Fig. 3b, Table 5).

Table 4 Spearman's correlation (*rho*) between qEEG power and CERAD-K in patients with AD ($N = 30$)

		MMSE-KC	SBT-K	TMT A	TMT B	Word list			Constructional		K-BNT	Word fluency
						Memory	Recall	Recognition	Praxis	Recall		
Global	Delta	−0.245	0.350	0.064	0.179	−0.147	0.296	−0.042	−0.106	−0.157	−0.036	−0.211
	Theta	−0.422*	0.274	0.117	0.254	−0.290	−0.054	−0.267	−0.153	−0.193	−0.112	−0.267
	Alpha	−0.022	0.052	0.168	0.015	−0.063	−0.153	−0.141	−0.004	−0.026	0.021	0.010
	Beta	0.505**	−0.447*	−0.402*	−0.045	0.408*	0.020	0.275	0.454*	0.270	0.223	0.129
	Gamma	−0.052	−0.024	0.023	−0.209	0.010	0.095	0.249	−0.136	0.054	−0.141	0.206
Frontal left	Delta	−0.219	0.291	0.015	−0.025	−0.140	0.071	−0.193	−0.230	−0.276	−0.124	−0.286
	Theta	−0.290	0.265	0.017	0.270	−0.293	−0.082	−0.271	−0.197	−0.122	−0.076	−0.264
	Alpha	−0.019	0.062	0.149	0.310	−0.112	−0.133	−0.119	−0.081	0.003	0.085	−0.086
	Beta	0.429*	−0.404*	−0.354	−0.061	0.358	−0.008	0.204	0.247	0.513**	0.320	0.086
	Gamma	−0.025	0.000	0.098	−0.325	0.026	0.068	0.172	0.048	−0.109	−0.131	0.287
Frontal right	Delta	−0.323	0.387*	0.182	0.102	−0.215	0.188	−0.169	−0.112	−0.204	−0.131	−0.292
	Theta	−0.422*	0.315	0.186	0.165	−0.348	−0.098	−0.299	−0.158	−0.246	−0.212	−0.342
	Alpha	−0.098	0.164	0.181	0.195	−0.142	−0.132	−0.170	−0.072	−0.070	0.034	−0.113
	Beta	0.361	−0.404*	−0.321	0.029	0.332	−0.099	0.128	0.255	0.407*	0.224	0.068
	Gamma	0.085	−0.085	−0.008	−0.415*	0.123	0.111	0.189	0.096	−0.015	−0.064	0.277
Central left	Delta	−0.172	0.361	0.122	0.347	−0.205	0.217	−0.160	−0.063	−0.147	−0.005	−0.269
	Theta	−0.277	0.231	0.109	0.372*	−0.153	−0.014	−0.280	−0.132	−0.130	0.029	−0.122
	Alpha	0.134	−0.011	0.175	0.079	0.086	−0.053	−0.135	0.038	0.026	0.098	−0.019
	Beta	0.498**	−0.459*	−0.386*	−0.138	0.420*	0.022	0.263	0.279	0.438*	0.195	0.185
	Gamma	−0.133	−0.135	−0.065	−0.144	−0.205	−0.052	0.269	−0.098	−0.105	−0.105	0.268
Central right	Delta	−0.346	0.467*	0.065	0.204	−0.272	0.120	−0.192	−0.123	−0.174	−0.155	−0.231
	Theta	−0.518**	0.420*	0.178	0.359	−0.414*	−0.175	−0.335	−0.206	−0.327	−0.257	−0.292
	Alpha	−0.119	0.047	0.240	0.232	−0.114	−0.135	−0.161	−0.025	−0.021	0.041	−0.137
	Beta	0.544**	−0.549**	−0.403*	−0.099	0.412*	−0.003	0.268	0.243	0.395*	0.252	0.196
	Gamma	0.083	−0.073	−0.096	−0.440	0.006	0.093	0.221	0.026	0.023	−0.013	0.299
Occipital left	Delta	−0.200	0.209	0.005	0.138	−0.210	0.306	0.100	−0.074	−0.074	−0.011	−0.215
	Theta	−0.371*	0.180	0.075	0.321	−0.228	−0.006	−0.248	−0.153	−0.083	−0.035	−0.164
	Alpha	−0.017	0.081	0.145	0.091	−0.070	−0.184	−0.153	0.009	−0.060	−0.069	−0.015
	Beta	0.444*	−0.407*	−0.370*	−0.126	0.422*	0.061	0.248	0.307	0.396*	0.156	0.027
	Gamma	−0.091	0.052	0.124	−0.297	−0.036	0.072	0.063	0.094	−0.082	−0.113	0.138
Occipital right	Delta	−0.103	0.290	−0.031	0.242	−0.178	0.410*	0.091	−0.030	−0.125	0.058	−0.231
	Theta	−0.413*	0.238	0.094	0.398*	−0.359	−0.036	−0.203	−0.251	−0.128	−0.049	−0.185
	Alpha	0.029	−0.011	0.100	0.026	−0.075	−0.145	−0.073	−0.045	0.019	−0.003	0.029
	Beta	0.514**	−0.473**	−0.420*	−0.138	0.470**	0.040	0.292	0.254	0.449*	0.211	0.150
	Gamma	−0.066	0.093	0.139	−0.258	0.044	0.120	0.036	0.195	−0.095	−0.167	0.113

qEEG quantitative electroencephalography, *MMSE-KC* Mini-Mental State Examination in CERAD-K, *SBT-K* Korean version of the short blessed test, *TMT* trail making test, *K-BNT* Korean version of the Boston naming test

* $p < 0.05$; ** $p < 0.01$

The regional CSD of the theta band, which was significantly different between the AD and NC groups and between moderate AD patients and NC subjects, was averaged for each gyrus. Table 6 shows the correlation patterns between the CSD of the theta band and the CERAD-K test scores in AD patients. Significant correlations were mainly found in the right temporal region. The highest correlation in the AD patients was between the CSD of the theta band in the transverse temporal gyrus and the SBT-K scores ($r = 0.575$, $p < 0.01$; Table 6).

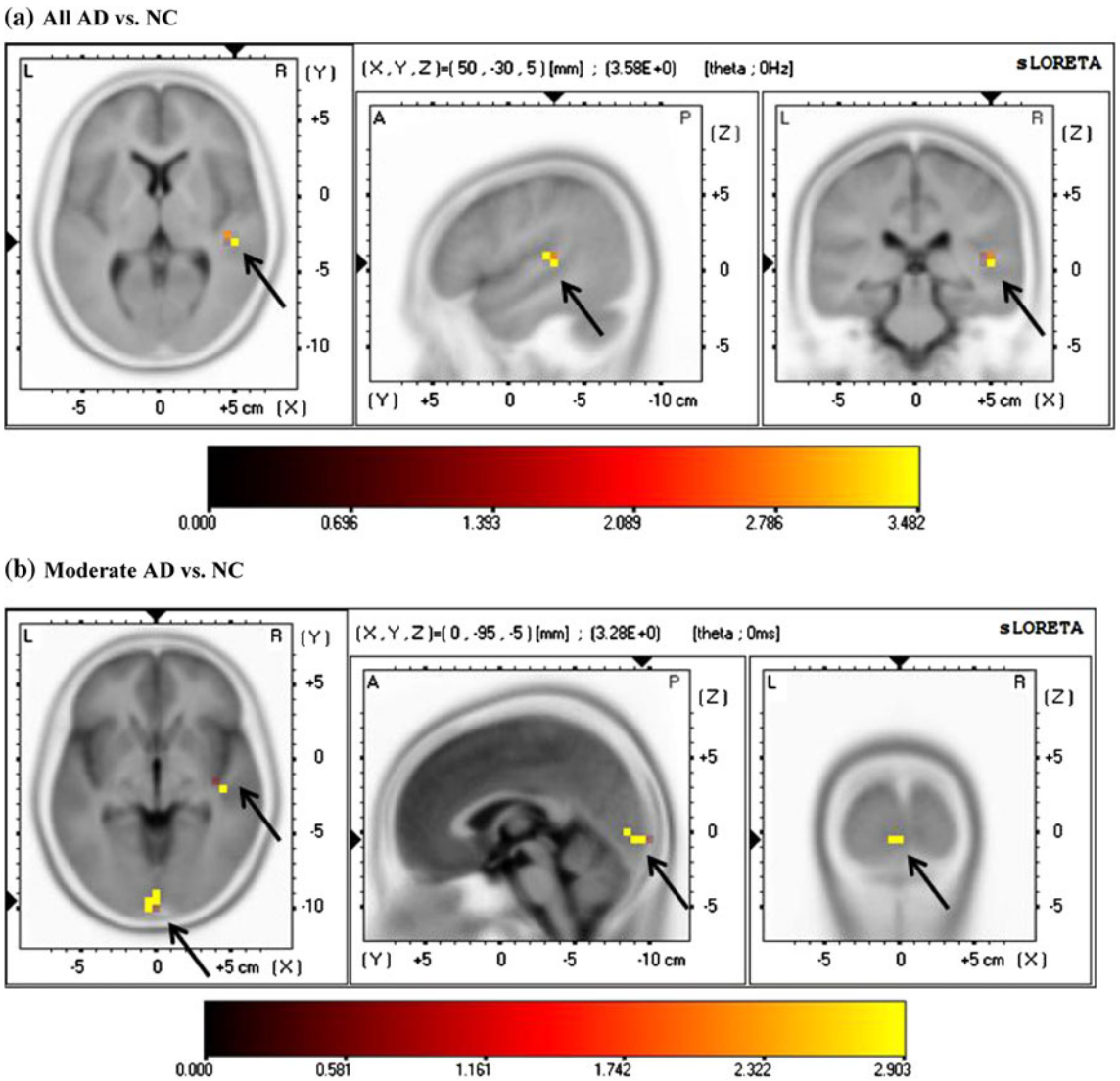

Fig. 3 (**a**) The source activity for the theta band of all patients with AD ($N = 30$) shows higher activation in the right temporal gyrus compared to NC subjects ($N = 30$). The voxels marked *yellow* and *orange* show significant increase of source activation ($p < 0.05$, two-tailed). (**b**) The source activity for theta band of the patients with moderate severity AD ($N = 13$) shows higher activation in the right temporal and left occipital gyrus compared to NC subjects ($N = 30$). The voxels marked *yellow* and *orange* show a significant increase of source activation ($p < 0.05$, one-tailed)

Lateral Asymmetry of qEEG Power

Table 7 shows the LAI among the mild AD, moderate AD, and NC groups for the frontal, central, and occipital regions. A change in dominance indicated a trend in the change of qEEG power from the NC subjects to the mild to moderate AD patients. In the frontal region, alpha power dominance moved from the left to the right between the NC and moderate AD groups (0.005 ± 0.03 vs. -0.022 ± 0.04, respectively, $p < 0.05$). In the central region, alpha power dominance moved from the right to the left between the NC and moderate AD groups (-0.051 ± 0.09 vs. 0.023 ± 0.10, respectively, $p < 0.05$). Beta power dominance moved from the right to the left between the NC and moderate AD groups (-0.021 ± 0.04 vs. 0.019 ± 0.04, respectively, $p < 0.05$). Gamma power dominance moved from the left to the right between the NC and moderate AD groups (0.05 ± 0.08 vs. -0.061 ± 0.16, respectively, $p < 0.05$). In the occipital region, theta power dominance moved from the left to the right between the NC and moderate AD groups (0.003 ± 0.04 vs. -0.072 ± 0.10, respectively, $p < 0.05$). Gamma power dominance moved from the right to the left between the NC and moderate AD groups (-0.019 ± 0.08 vs. 0.091 ± 0.08, respectively, $p < 0.05$).

Table 5 Regions of significant difference in theta power-CSD between AD patients and NC subjects and between moderate severity AD patients and NC subjects

	Lobe	Gyrus	Brodmann Area	MNI coordinate		
				X	Y	Z
All AD versus NC*	Right temporal	Superior temporal gyrus	13	45	−20	10
	Right temporal	Transverse temporal gyrus	41	45	−25	10
Moderate AD versus NC**	Occipital	Lingual gyrus	18	0	−95	−5
	Right temporal	Transverse temporal gyrus	41	50	−25	10
	Right temporal	Superior temporal gyrus	13	45	−20	5
	Right sub-lobar	Insula	13	45	−15	5
	Right parietal	Postcentral gyrus	40	50	−25	15
	Left occipital	Cuneus	17	−5	−100	−5

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*Two-tailed, $p < 0.05$; **one-tailed, $p < 0.05$

Table 6 Spearman's correlation (*rho*) between the CERAD-K in AD patients ($N = 30$) and brain regions showing significant differences of theta power-CSD between AD patients and NC subjects

	Right temporal lobe		Right sub-lobar	Right parietal lobe	Left occipital lobe	
	Superior temporal gyrus	Transverse temporal gyrus	Insula	Postcentral gyrus	Cuneus	Lingual gyrus
MMSE-KC	−0.482**	−0.403*	−0.285	−0.300	−0.280	−0.511**
SBT-K	0.413*	0.575**	0.425*	0.436*	0.419*	0.379*
TMT A	0.310	0.207	0.023	0.035	0.035	0.284
TMT B	0.255	0.164	0.163	0.229	0.242	0.099
Word list memory	−0.295	−0.371*	−0.213	−0.238	−0.181	−0.267
Word list recall	−0.291	−0.190	−0.195	−0.147	−0.083	−0.325
Word list recognition	−0.108	−0.314	−0.276	−0.260	−0.219	−0.172
Constructional praxis	−0.368*	−0.199	−0.102	−0.088	−0.083	−0.338
Constructional recall	−0.013	−0.181	−0.103	−0.165	−0.090	−0.020
K-BNT	−0.456*	−0.264	−0.169	−0.144	−0.137	−0.496**
Word fluency	−0.167	−0.432*	−0.226	−0.280	−0.249	−0.264

MMSE-KC Mini-Mental State Examination in CERAD-K, *SBT-K* Korean version of the short blessed test, *TMT* trail making test, *K-BNT* Korean version of the Boston naming test

Correlation is significant at the 0.01 level **(two-tailed) and at the 0.05 level *(two-tailed)

Discussion

The present study investigated the differences in qEEG and CSD among mild AD patients, moderate AD patients, and NC subjects, and explored the relationships between the values of qEEG and CSD and neuropsychological test scores in AD patients. No significant differences were observed between NC and mild AD. We found that there were significant differences in the power of the theta and beta qEEG bands between moderate AD patients and NC subjects. The CSD of the theta band in the AD group was significantly higher than that of the NC group in the temporal, parietal, and occipital regions. In addition, the qEEG and averaged CSD of the theta band had a significant functional correlation with the neuropsychological test scores of CERAD-K in the AD patients.

Consistent with previous finding, we found that AD patients showed significantly increased power of the theta band and decreased power of the beta band compared with NC subjects. Furthermore, when moderate AD patients were compared with NC subjects, these changes in the power of the theta and beta bands became more prominent. The beta band is thought to be related to excitatory activity and cognitive processes, which are impaired in AD patients (Holschneider and Leuchter 1995; Koenig et al. 2005). In addition, beta activity was significantly correlated with early cognitive decline in normal elderly people (Williamson et al. 1990). Additionally, the theta wave is known

Table 7 Comparison of the LAI of the relative power of the delta, theta, alpha, beta, and gamma frequency bands among patients with mild and moderate severity AD and NC subjects. Dominance change indicates a change of qEEG power from NC to mild to moderate AD. One-way ANOVA was performed with post hoc LSD method. Significant differences are indicated with asterisks

		LAI of mild AD ($N = 17$)	LAI of moderate AD ($N = 13$)	LAI of NC ($N = 30$)	p	Dominance change
Frontal	Delta	0.003 ± 0.07	0.016 ± 0.06	−0.003 ± 0.06	0.66	
	Theta	−0.014 ± 0.05	−0.015 ± 0.06	0.002 ± 0.04	0.47	
	Alpha	0.003 ± 0.04	−0.022 ± 0.04	0.005 ± 0.03	0.01[c]	L → R
	Beta	−0.002 ± 0.03	−0.016 ± 0.02	−0.003 ± 0.02	0.23	
	Gamma	0.011 ± 0.06	0.044 ± 0.07	−0.001 ± 0.05	0.10	
Central	Delta	−0.008 ± 0.11	−0.010 ± 0.14	0.024 ± 0.10	0.53	
	Theta	0.044 ± 0.07	0.063 ± 0.10	0.030 ± 0.06	0.44	
	Alpha	−0.055 ± 0.05	0.023 ± 0.10	−0.051 ± 0.09	0.02[a,c]	L ← R
	Beta	0.004 ± 0.05	0.019 ± 0.04	−0.021 ± 0.04	0.04[c]	L ← R
	Gamma	0.031 ± 0.07	−0.061 ± 0.16	0.050 ± 0.08	0.00[a,c]	L → R
Occipital	Delta	0.005 ± 0.09	−0.012 ± 0.13	0.026 ± 0.07	0.45	
	Theta	0.007 ± 0.05	−0.072 ± 0.10	0.003 ± 0.04	0.00[a,c]	L → R
	Alpha	0.015 ± 0.07	−0.048 ± 0.08	−0.018 ± 0.05	0.05	
	Beta	0.008 ± 0.04	−0.020 ± 0.03	0.007 ± 0.03	0.07	
	Gamma	−0.029 ± 0.09	0.091 ± 0.16	−0.019 ± 0.08	0.00[a,c]	L ← R

[a] between mild AD and moderate AD

[b] between mild AD and NC

[c] between moderate AD and NC

to be involved in memory, synaptic plasticity, top down control, and long-range synchronization (Gevins et al. 1997; Huerta and Lisman 1993; Vertes 2005; Von Stein et al. 2000). Furthermore, increased theta wave activity is thought to reflect drowsy mentality (Fernandez-Bouzas et al. 1999; Lee et al. 2006). Interestingly, increased theta wave activity, relative to healthy elderly controls, has been continuously reported in AD patients, which is considered to be an indicator of impaired cognitive processing (Bennys et al. 2001; Gianotti et al. 2007; Jung et al. 2007; Maurer and Dierks 1992; Schreiter-Gasser et al. 2008).

In the present study, the power of the theta and beta bands was correlated with neuropsychological function in AD patients. The power of the theta band was negatively correlated with MMSE-KC test scores. The power of the beta band was positively correlated with MMSE-KC, word list memory, and constructional praxis test scores, and negatively correlated with SBT-K and TMT. These findings are suggesting that the power of the theta and beta bands may reflect impaired cognitive function in the mild to moderate stage of AD. AD proceeds in stages, with particular cognitive malfunctions observed at each stage. For instance, memory and learning impairments are usually notable in the early stages of dementia (Förstl and Kurz 1999; Jeong 2004). Language, judgment, abstract reasoning, logical reasoning, and planning are damaged gradually in the later stages of dementia (Bianchetti and Trabucch 2001). In our study, the decrease in the power of the beta band in AD patients was associated with impaired functional capacity in global cognition, memory, visuospatial function, and attention, which typically appear in the early stages of AD. However, the decrease in the power of the beta band was not associated with impairments in language or executive function, which appear in the later stages of AD. Furthermore, the AD patients in the present study did not show abnormal activity in the alpha and delta bands, which are supposed to be implicated in the abnormalities associated with the later stages of AD (Jeong 2004). To confirm these results, further studies are necessary on subjects in the later stages of AD.

There were significant increases in the CSD of the theta band in the superior temporal gyrus (BA 13 and 22) and the transverse temporal gyrus (BA 41) of the right hemisphere in the AD patients. Our result showing that increased theta wave activity that could be traced back to increased activity in the temporal areas is in line with previous findings. Jacobs et al. (2011) reported that medial temporal lobe atrophy was the best predictive factor in determining the cognitively stability of AD patients. It has been suggested that beta-amyloid deposition (Armstrong 2010) and the concentration of neuritic plaques (Marshak et al. 1992) in the temporal lobe can be useful diagnostic tools for AD. Peters et al. (2009) reported that AD patients showed reduced activation in several regions during the encoding phase, including the transverse temporal gyri. Furthermore, increased slow wave activity in the temporal lobe of AD patients has been

reported repeatedly. Jung et al. (2007) reported that maximal different areas of slow wave activity between AD and NC groups were observed in the right parieto-temporal region. Gianotti et al. (2007) also reported increased theta activity of AD patients in the temporal, parietal, and occipital areas. Sherlin (2009) reported that AD patients showed significant increases in the delta and theta bands in the right temporal lobe and the cingulate gyrus, respectively, compared with an age- and sex-matched control group.

In the present study, CSD in the superior temporal gyrus (BA 13 and 22) and the transverse temporal gyrus (BA 41) of the right hemisphere had a significant positive correlation with the MMSE-KC and SBT-K test scores, which reflect global cognition in AD patients. CSD in the superior temporal gyrus was also significantly correlated with constructional praxis and K-BNT, which reflect visuospatial and language function, respectively. The transverse temporal gyrus also had a significant correlation with word fluency and word list memory, which reflect executive and memory function, respectively. The superior temporal gyrus and transverse temporal gyrus have been suggested to be important regions for learning and memory registration (Nelson et al. 2009). Neuroimaging studies have indicated that AD patients suffer from brain damage in these regions. For example, Frisoni et al. (2007) reported a 25 % reduction in the gray matter of restricted areas of the right superior temporal gyrus and the medial temporal lobe in patients with late onset AD. Peters et al. (2009) found reduced activity in the transverse temporal gyrus during a verbal short-term memory recognition task in AD patients. Taken together, a significant increase in the CSD of the theta bands in the superior temporal gyrus (BA 13 and 22) and the transverse temporal gyrus (BA 41) of the right hemisphere may be associated with the impaired orientation, memory, and concentration exhibited by AD patients.

Our results also suggest that the occipital lingual gyrus, cuneus, postcentral gyrus, and insular regions could be implicated in AD. Previous neuroimaging studies showed that these regions are repeatedly associated with disease progress and functional decline in AD patients. Recently, Kinkingnéhun et al. (2008) revealed that the medial occipitoparietal areas, especially in the precuneus, lingual gyrus, cuneus, and the surrounding cortex of the parieto-occipital sulcus, could be vulnerable regions in quickly declining AD patients compared with slowly declining AD patients. Devanand et al. (2006) also reported that AD patients showed hyperperfusion in the bilateral insula, lingual gyri, and cuneus compared with healthy controls in their positron emission tomography study. Nobili et al. (2009) also reported that technetium-99m *N*,*N*-1,2-ethylenediylbis-L-cysteine diethyl ester dihydrochloride single-photon emission computed tomography showed a significant correlation between the left postcentral gyrus and the verbal memory test in AD patients.

With respect to laterality, the right hemisphere is known to be more vulnerable to AD than the left hemisphere. Brain perfusion abnormalities were found to be lateralized in the right hemisphere in a minimal cognitive impairment to AD conversion group (Chetelat et al. 2003; Habert et al. 2011). The earlier involvement of the right hemisphere compared to the left hemisphere was previously found on the basis of neuropsychological (Goldstein and Shelly 1981) and structural (Good et al. 2001) data, thus possibly explaining the asymmetric CSD in our AD patients. However, there were no consistent and reliable results for the laterality (LAI) of cortical regional qEEG. Our data suggest that CSD could be a better means to evaluate the laterality of brain activity compared to cortical qEEG power.

Our study has some limitations that need to be addressed. First, the AD and NC groups had a significantly greater proportion of female subjects. However, it was revealed that AD is more prevalent in females (Andersen et al. 1999; Kim et al. 1999), while a few authors have stated that the prevalence was higher in males (Li et al. 1989; Rocca et al. 1990; Wang et al. 2000). Our data are supposed to reflect mainly the characteristics of the disease itself. Secondly, the present study was a cross-sectional study. A longitudinal approach could be useful to investigate the cognitive impairments and their qEEG correlates in AD patients over a period of time. Thirdly, the patients in the present study had mild to moderate AD. Patients with severe AD were not enrolled in the present study because they would not be able to tolerate the EEG test. Furthermore, mild AD with GDS 3 could be classified as MCI. Therefore, the lack of significant differences between the NC and mild AD group might have been influenced by the inclusion of the MCI group. Despite its limitations, this study suggests that the theta and beta bands are significantly implicated in the severity of symptoms in AD patients. Therefore, we conclude that qEEG and CSD can serve as valuable biological markers to evaluate the severity of symptoms in AD patients.

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Conflict of interest None to declare.

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