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Region and frequency specific changes of spectral power in Alzheimer's disease and mild cognitive impairment

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HIGHLIGHTS

- Theta and delta band spectral powers tended to increase in selected scalp regions according to cognitive impairment from normal to Alzheimer's disease (AD) via amnestic mild cognitive impairment (aMCI), whereas alpha and beta 2 band powers showed a decreasing tendency.
- Spectral powers with an increasing or decreasing pattern correlated with subcategories of the neuropsychological tests.
- Region and frequency specific oscillatory characteristics of EEG reflect domain-specific cognitive function in patients with aMCI and AD.

ABSTRACT

Objectives: To find out whether healthy control (HC), amnestic mild cognitive impairment (aMCI), and Alzheimer's disease (AD) subjects exhibit region and frequency specific spectral power differences and whether the spectral power changes correlate with domain-specific cognitive function.
Methods: Forty-one AD, 38 aMCI, and 39 HC subjects underwent quantitative EEG and comprehensive neuropsychological tests. Repeated measures analysis of variance was performed to identify differences in EEG spectral power among the three groups by scalp region and EEG frequency. Correlations between region and frequency specific spectral powers and neuropsychological test scores were evaluated.
Results: Temporal and parieto-occipital theta band powers were highest in AD. Whereas, parieto-occipital alpha and frontal and temporal beta 2 band powers were highest in HC and lowest in AD ($p < 0.05$). Temporal and parieto-occipital theta powers negatively correlated with verbal and visuospatial memory recall, while parieto-occipital alpha and temporal beta 2 powers positively correlated with verbal memory recall ($p < 0.01$).
Conclusions: Region and frequency specific oscillatory characteristics of EEG reflect domain-specific cognitive function in patients with aMCI and AD.
Significance: Region and frequency specific spectral powers have clinical implications as additional markers differentiating AD, aMCI, and HC.

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder in the elderly (Blennow et al., 2006; Cummings, 2004; Kelley and Petersen, 2007), whereas mild cognitive impairment (MCI) is a syndrome with clinical and pathological characteristics that represent a transition state between normal aging and AD (Gauthier et al., 2006; Kelley and Petersen, 2007). Definitive diagnosis cannot be made for either disease until a brain biopsy has been performed (Blennow et al., 2006; Cummings, 2004;

Abbreviations: aMCI, amnestic mild cognitive impairment; AD, Alzheimer's disease; Lt_F, left frontal region; Rt_F, right frontal region; Lt_T, left temporal region; Rt_T, right temporal region; Lt_PO, left parieto-occipital region; Rt_PO, right parieto-occipital region.

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Gauthier et al., 2006; Kelley and Petersen, 2007). Given the evidence that the early detection and management of AD and MCI may delay irreversible cognitive deterioration, early diagnoses of both diseases are challenging (Blennow et al., 2006; Cummings, 2004; Gauthier et al., 2006; Kelley and Petersen, 2007). Many trials have been conducted using biological or imaging markers to improve the diagnostic accuracy of AD and MCI (Perrin et al., 2009), but none of these markers is definitive, yet. Furthermore, most neuroimaging studies are expensive and biological workups require invasive procedures.

Quantitative analysis of digital EEG (QEEG) has been introduced as a non-expensive, non-invasive, and objective tool for evaluating dementia. Longitudinal analyses of brain EEG rhythms have produced objective evidences of disease progression from MCI to AD (Coben et al., 1985; Huang et al., 2000; Jelic et al., 2000; Luckhaus et al., 2008; Rossini et al., 2006). One typical EEG change in patients with AD is the slowing of EEG rhythms. The earliest changes are an increase in theta band power and a decrease in beta power, followed by a decrease in alpha power. Delta power is known to increase during the later stages of AD (Coben et al., 1985; Jeong, 2004). However, most QEEG studies in AD have focused on the slowing of rhythms with respect to general cognitive function assessment, such as mini-mental status examination (MMSE) and did not perform detailed neuropsychological tests. On the other hand, QEEG studies in which neuropsychological tests were performed did not describe specific brain regions in association with domain-specific cognitive function changes (Babiloni et al., 2007; Lindau et al., 2003; van der Hiele et al., 2007a). QEEG studies that focused on brain area have described spectral power changes in the temporal and frontal scalp regions (Duffy et al., 1984) or temporal and parietal scalp regions in AD (Breslau et al., 1989). Another study using low resolution brain electromagnetic tomography (LORETA) showed changes in temporo-parietal regions in AD (Gianotti et al., 2007). However, the region-specific EEG changes noted in previous studies need to be interpreted in line with detailed neuropsychological tests to better understand their clinical implications.

In AD and MCI patients, memory impairment is the most common initial manifestation, while other cognitive functions, such as visuospatial function, praxis, language, and execution usually deteriorate after amnesia (Kelley and Petersen, 2007). Pathologic and imaging studies support the clinical findings such that the hippocampus and medial temporal lobe begin to degenerate during the early stage of AD and then other association cortices degenerate, thereafter (Perrin et al., 2009). Given the slowing of EEG rhythms and the hierarchical deterioration of brain structures according to the severity of AD, to evaluate the frequency and region specific QEEG changes in association with cognitive domain specific neuropsychological tests would be informative. Therefore, in this study, we evaluated EEG spectral power in HC subjects, amnestic MCI (aMCI) patients, and AD patients to determine; (1) whether QEEG frequencies and spectral powers differ by scalp region in these three groups, and (2) whether there is a correlation between the region- and frequency-specific spectral powers and neuropsychological test scores.

2. Methods

2.1. Subjects

The subjects of the present study were recruited from the outpatient memory disorder clinic at the Korea University Ansan Hospital and the Ansan GEriatric (AGE) cohort (Han et al., 2009) from January 2007 to October 2008. Out of 85 AD, 43 aMCI, and 19 HC subjects, we enrolled those who underwent the QEEG, had more than nine 1.5-s-epochs to interpret, and did not reveal an EEG abnormality. An EEG abnormality was defined as asymmetry of background activity, continuous theta range slow waves, generalized or focal delta range slow waves, or epileptiform discharges. Forty-one of the 85 AD patients, 38 of the 46 aMCI patients, and 6 of the 19 HC subjects were enrolled. Age- and sex-matched 33 HC subjects were further enrolled from the AGE cohort during the same period and finally 39 HC subjects were included in this study. Patients taking cholinesterase inhibitors, benzodiazepines, or antidepressants that could influence EEG rhythms were not included (Babiloni et al., 2006d). Informed, written consent for participation was obtained from each individual and the Institutional Review Board of the Korea University Ansan Hospital approved the study protocol.

2.2. Diagnostic criteria

Each subject underwent general medical and neuropsychological assessments and laboratory analyses, including, CBC, chemistry, vitamin B12/folate, syphilis serology, and thyroid function tests. Trained research nurses administered the neuropsychological tests to each subject. Diagnoses of probable AD and aMCI were made by two experienced neurologists (R.J.H. and P.M.H.). Probable AD was diagnosed according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) (McKhann et al., 1984). aMCI was diagnosed based on the criteria proposed by Peterson: (1) memory complaint, preferably corroborated by an informant; (2) memory impairment for age and education; (3) essentially normal general cognitive function; (4) largely preserved activities of daily living; and (5) not demented (Petersen et al., 1999; Gauthier et al., 2006; Kelley and Petersen, 2007).

2.3. Neuropsychological tests

The Korean version of the Consortium to Establish A Registry for Alzheimer's Disease (CERAD-K) (Lee et al., 2002; Morris et al., 1989) and Digit Span Test (Tulsky and Ledbetter, 2000) were used for neuropsychological evaluations. CERAD-K is comprised of eight sub-tests: Verbal Fluency, Boston Naming Test (BNT), MMSE, Word List Memory, Constructional Praxis, Word List Recall, Word List Recognition, and Constructional Recall (Lee et al., 2002). Verbal memory was assessed using Word List Memory, Word List Recall, and Word List Recognition tasks, while visuospatial memory was evaluated using Constructional Recall task. Visuospatial function was evaluated using Constructional Praxis task and language function was evaluated by Verbal Fluency and the BNT. The Digit Span Test was performed to evaluate attention (Tulsky and Ledbetter, 2000). The clinical dementia rating scale (CDR) (Morris, 1993) and the global deterioration scale (GDS) (Reisberg et al., 1982) were also performed.

2.4. EEG recordings

EEG was recorded under waking-rest conditions (eyes-closed) from 19 scalp electrodes positioned according to the International 10–20 System (Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, O2) referenced to Pz electrode. Then EEG signals obtained were re-referenced to a common average montage as described previously (Yum et al., 2008; Jung et al., 2009). EEG was recorded in a quiet room, under dim light, at normal room temperature (20 ± 2 °C). State of vigilance was controlled by the online visual inspection of EEG traces during recording sessions and drowsiness of each subject was avoided by issuing verbal alerts. Impedance was kept below 5 kΩ, and the bandpass filter was set at 0.3–70 Hz with a sampling rate of 200 Hz. EEG for analyses were

recorded in the waking state with eyes closed and artifact-free 1.5-s epochs were identified. Nine to twelve epochs were finally obtained per patient. Fast Fourier Transform (FFT)-based spectral analysis computed spectral power for five frequency bands [delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta 1 (13–21 Hz), and beta 2 (22–30 Hz)]. One independent investigator blinded to the diagnosis of subjects visually confirmed that the EEG segments were acceptable for further analyses.

2.5. Spectral power analysis

FFT-based spectral power analysis (Hanning windowing function, no phase shift) was used to compute the power densities of EEG rhythms at a frequency resolution of 0.78 Hz (range from 0 to 30 Hz). Absolute power for each of the five frequency bands was determined and divided by the sum of the overall spectral powers of each subject in order to obtain relative powers. Relative powers were log-transformed prior to statistical analysis. The electrodes were grouped into six scalp regions: the left frontal (Fp1, F7, F3), right frontal (Fp2, F8, F4), left temporal (T7, C3), right temporal (T8, C4), left parieto-occipital (P3, P7, O1), and the right parieto-occipital (P4, P8, O2) regions.

2.6. Statistical analysis

2.6.1. Demographics and neuropsychological tests

One-way analysis of variance (ANOVA) or the Kruskal–Wallis test was used to compare variables among the groups. Variables that fulfilled the two preconditions of ANOVA, (i) a normal distribution and (ii) homogeneity of variance, were used for one-way ANOVA followed by Bonferroni's post hoc test for multiple pairwise comparisons. Other variables were analyzed using the Kruskal–Wallis test followed by Bonferroni's post hoc test for multiple comparisons of mean ranks. Normally distributed variables are presented as means ± SDs and non-normally distributed variables are presented as medians and interquartile ranges (IQR; 25th–75th percentile). Statistical significance was accepted for p value of <0.05.

2.6.2. EEG spectral power

Regional spectral power from HC, aMCI, and AD subjects were used as input data for three-way repeated measures ANOVA. Age, gender, and duration of education served as covariates. Because Mauchly's criterion for the assumption of sphericity was violated, Greenhouse-Geisser adjusted degrees of freedom were used. Group (3 levels: HC, aMCI, AD) served as the between-subjects factor, while Frequency Band (5 levels: delta, theta, alpha, beta 1, beta 2) and scalp region (6 levels: left frontal, right frontal, left temporal, right temporal, left parieto-occipital, and right parieto-occipital region) served as within-subject factors. Least square MEANS (LSMEANS) analysis in the SAS software package was used for the post hoc analyses of interaction effects between factors considered ($p < 0.05$).

2.6.3. Correlation between QEEG analyses and neuropsychological tests

Pearson's correlation analysis was performed to evaluate the correlations between neuropsychological test scores and spectral powers which represented linear changes among the three groups. Additional Pearson's correlation analysis between the spectral power and neuropsychological test scores was performed in each diagnostic group to see whether the correlation exists within each group. For the correlation analysis, a cut-off p value of less than 0.01 was applied. Statistical analyses were performed using the SPSS (release 12.0; Chicago, IL) and SAS (release 9.0: Chicago, IL) program.

3. Results

3.1. Demographics and clinical characteristics of the patients

Demographics and clinical characteristics of the patients are detailed in Table 1. No difference in demographics was observed among the groups, except duration of education. Duration of education, age, and sex were used as covariates in repeated measures ANOVA. The median values (IQR) of the CDR differed among the three groups: HC (0.0, 0.0–0.0), aMCI (0.5, 0.5–0.5), and AD (1.0, 0.5–1.0) ($p < 0.01$). The median values (IQR) of GDS also differed among the groups: HC (2.0, 1.0–2.0), aMCI (3.0, 2.0–3.0), and AD (4.0, 4.0–5.0) ($p < 0.01$). The neuropsychological test findings of the three diagnostic groups are presented in Table 2.

3.2. Regional and frequency specific power spectra

Spectral power maps for HC, aMCI, and AD subjects in each frequency band are shown in Fig. 1. Delta power in the parieto-occipital scalp region in the AD group was higher than that in the HC group (Fig. 2A). The theta band in the temporal and parieto-occipital scalp regions showed that spectral power tended to be highest in AD patients and progressively decreased in aMCI and HC subjects (Fig. 2B). Alpha band power in the parieto-occipital scalp region was highest in the HC subjects and progressively decreased in aMCI and AD patients (Fig. 2C). The beta 1 band power findings varied among groups, but beta 2 band power was highest in the HC and decreased in the aMCI and AD subjects in the frontal and temporal scalp regions (Fig. 2D).

Table 1
Demographic and clinical characteristics by diagnostic group.

	Control group ($N = 39$)	aMCI group ($N = 38$)	AD group ($N = 41$)	p-Value
Mean age, years (±SD)[a]	72.7 ± 4.3	72.2 ± 5.7	73.8 ± 5.8	0.442
Sex (men: women)[b]	12: 27	13: 25	5: 36	0.053
Education, years (IQR)[c]	7.0 (2.0–14.0)*	6.5 (3.8–12.0)**	1.5 (0.0–6.0)*,**	<0.01
MMSE score (IQR)[c]	27 (25–28)***	24 (19–27)***	16 (12–18)***	<0.01

Abbreviations: aMCI, amnestic mild cognitive impairment; AD, Alzheimer's disease; IQR, interquartile range; MMSE: mini-mental status examination.
Data are presented as mean (±SD) for normally distributed variables and median (25th–75th percentile, IQR) for non-normally distributed variables.
[a] ANOVA followed by Bonferroni's post hoc test.
[b] χ^2 test.
[c] Kruskal–Wallis test followed by Bonferroni's post hoc test.
* Significant difference ($p < 0.01$) between AD and control group.
** Significant difference ($p < 0.01$) between AD and aMCI group.
*** Significant difference ($p < 0.01$) between AD and control group, between AD and aMCI group, and between aMCI and control group.

Table 2
Neuropsychological tests scores according to diagnostic group.

	Control group (N = 39)	aMCI group (N = 38)	AD group (N = 41)
Word List Memory (±SD)[a]	17.5 ± 4.1[¶]	11.9 ± 4.4[¶]	7.1 ± 3.1[¶]
Word List Recall (IQR)[b]	6.0 (5.0–7.0)[¶]	2.0 (0.8–3.0)[¶]	0.0 (0.0–0.0)[¶]
Word List Recognition (IQR)[b]	10.0 (9.0–10.0)[¶]	7.0 (4.8–9.0)[¶]	3.0 (1.0–7.0)[¶]
Constructional Praxis (IQR)[b]	10.0 (9.0–11.0)[*]	10.0 (7.0–11.0)[§]	7.0 (7.0–8.0)[*,§]
Constructional Recall (IQR)[b]	5.0 (4.0–8.0)[¶]	2.0 (0–5.0)[¶]	0.0 (0.0–1.5)[¶]
Verbal Fluency (±SD)[a]	13.9 ± 3.9[*]	12.3 ± 4.0[§]	8.2 ± 3.1[*,§]
Boston Naming Test (±SD)[a]	11.0 ± 2.5[¶]	9.1 ± 3.3[¶]	6.6 ± 2.7[¶]
Digit Span, Forward (IQR)[b]	5.0 (4.0–7.0)[*]	5.0 (4.0–6.0)[§]	4.0 (3.0–5.0)[*,§]
Digit Span, Backward (IQR)[b]	4.0 (3.0–4.0)[*]	3.0 (3.0–4.0)[§]	2.0 (0.0–3.0)[*,§]

Abbreviations: aMCI, amnestic mild cognitive impairment; AD, Alzheimer's disease; IQR, interquartile range.
Data are presented as mean (±SD) for normally distributed variables and median (25th–75th percentile, IQR) for non-normally distributed variables.
[a] ANOVA followed by Bonferroni's post hoc test.
[b] Kruskal–Wallis test followed by Bonferroni's post hoc test.
[*] Significant difference ($p < 0.01$) between AD and control group.
[§] Significant difference ($p < 0.01$) between AD and aMCI group.
[¶] Significant difference ($p < 0.01$) between AD and control group, between AD and aMCI group, and between aMCI and control group.

The main effects of within-subject factors [Frequency (F(2.83, 325.27) = 836.55, $p < 0.0001$), Scalp Region (F(1.95, 224.53) = 135.53, $p < 0.0001$)] and their interactions with between- subject factors [Frequency by Group (F(5.66, 325.27) = 4.18, $p < 0.0001$), Scalp Region by Group (F(3.91, 224.53) = 7.71, $p < 0.0001$)] were significant (Fig. 2). Age, sex, and duration of education did not influence the interactions as covariates. The significant interaction of frequency by Scalp Region by Group (F(10.87, 621.23) = 3.29, $p < 0.0001$) indicates that spectral power differs by frequency band in selected scalp regions. The scalp regions in which spectral power showed linear patterns of change, such as HC < aMCI < AD group or HC > aMCI > AD group, were selected in each frequency band ($p < 0.05$, LSMEANS post hoc test) (Fig. 2). Increasing patterns of spectral power from HC to AD were found in temporal scalp regions (theta frequency) and parieto-occipital scalp regions (delta and theta frequencies), while decreasing patterns of spectral power were found in frontal and temporal scalp regions (beta 2 frequency) and parieto-occipital scalp regions (alpha frequency). Spectral powers with increasing or decreasing patterns according to disease status were used for correlation analyses with neuropsychological test scores.

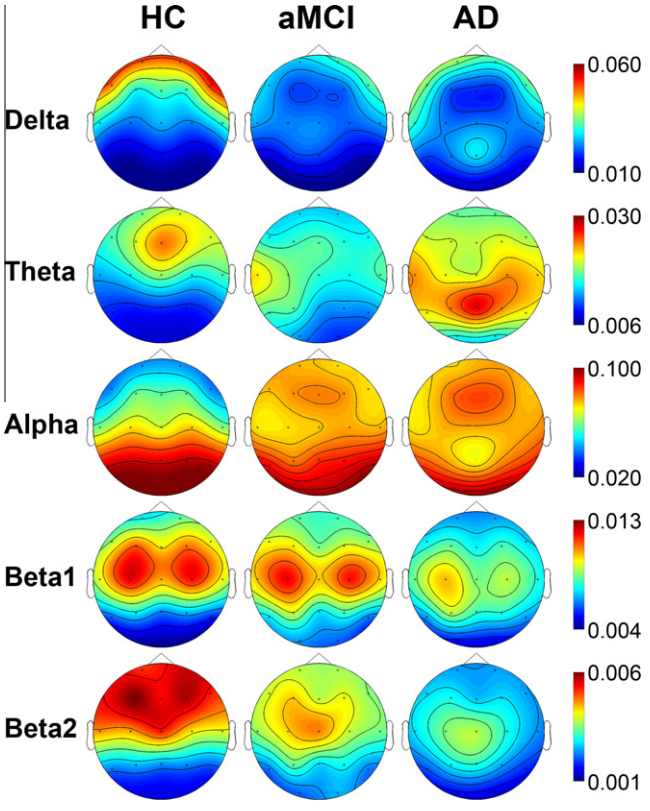

Fig. 1. EEG spectral power analysis represented in a statistical non-parametric map. The red color represents high spectral power, and the blue color represents low spectral power. The value in the bar represents absolute spectral power divided by summation of all the spectral powers obtained from all frequency bands of each subject. Rows represent the frequency bands: delta, theta, alpha, beta 1, and beta 2. Columns show the classification of subjects: healthy control (HC), amnestic mild cognitive impairment (aMCI), and Alzheimer's disease (AD). The left side of the map corresponds to the left hemisphere. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.3. Correlations between neuropsychological tests and EEG spectral powers

MMSE scores positively correlated with spectral power in the temporal beta 2 (left, $r = 0.223$; right, $r = 0.293$, $p < 0.05$) and the parieto-occipital alpha (left, $r = 0.232$; right, $r = 0.206$, $p < 0.01$) band, but negatively correlated with temporal theta (left, $r = -0.328$; right, $r = -0.301$, $p < 0.01$), and parieto-occipital theta (left, $r = -0.298$; right, $r = -0.307$, $p < 0.01$) band spectral powers.

Negative correlations were found between temporal and parieto-occipital theta powers and verbal memory ($p < 0.01$) and between parieto-occipital theta power and visuospatial memory ($p < 0.01$). Parieto-occipital alpha and temporal beta 2 powers were positively correlated with verbal memory. More specifically, alpha power correlated with verbal memory registration and recall and beta 2 power correlated with verbal memory recall and recognition ($p < 0.01$). Attention tasks did not correlate with spectral power of any frequency band ($p > 0.05$) (Table 3).

Less correlation was noted between the neuropsychological tests and spectral powers within each diagnostic group. In AD group, only left parieto-occipital delta power negatively correlated with the Constructional Praxis (Supplementary Table S1). There was no correlation in aMCI group (Supplementary Table S2). In HC group, more correlations were noted than the other groups (Supplementary Table S3). Temporal theta band spectral power showed negative correlation with verbal and visuospatial memory and visuospatial function as shown in correlation analyses across diagnostic groups. On the other hand, parieto-occipital alpha power negatively correlated with Verbal Fluency while parieto-occipital delta power positively correlated with Verbal Fluency and BNT.

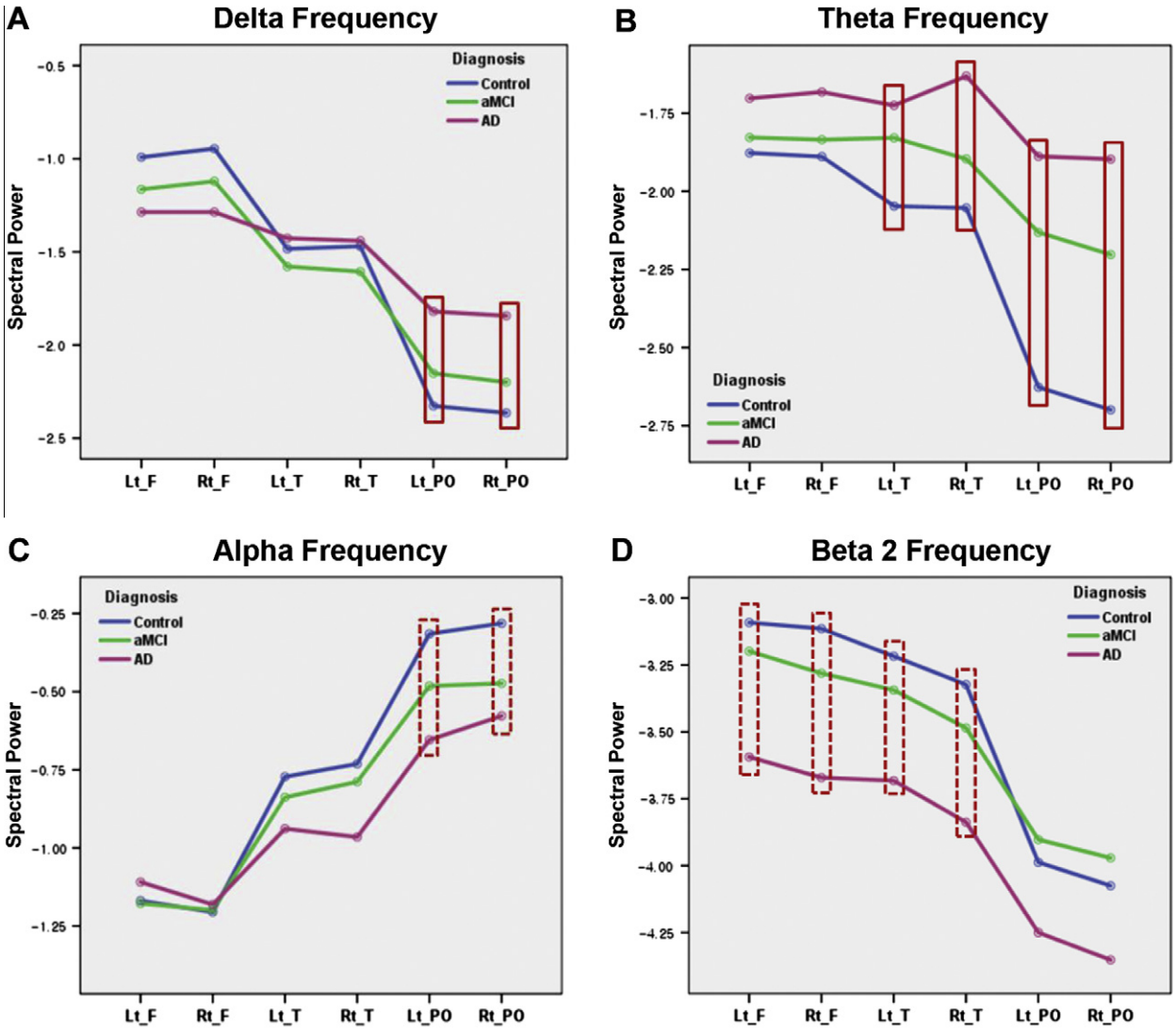

Fig. 2. EEG spectral power analysis relative to the interaction effects among the factors: group (control, aMCI, AD), band (delta, theta, alpha, beta 1, beta 2), and scalp regions (left frontal, right frontal, left temporal, right temporal, left parieto-occipital, and right parieto-occipital regions). The solid-line rectangles indicate the cortical regions and frequency bands in which spectral power presented statistically significant patterns in the following order: AD > aMCI > control (A and B), while dashed-line rectangles represent those in which spectral power presented statistically significant patterns in the following order: control > aMCI > AD (C and D) ($p < 0.05$, least square MEANS post hoc testing). The value in the *Y*-axis represents the estimated marginal means of spectral powers obtained from the General Linear Model of the SPSS software, version 12.0.

Table 3
Correlation coefficients between the EEG spectral power and neuropsychological tests.

	Word List Memory	Word List Recall	Word List Recognition	Constructional Praxis	Constructional Recall	Verbal Fluency	Boston Naming Test
Lt F beta 2	0.040	0.119	0.149	0.059	0.227*	0.024	0.005
Rt F beta 2	0.089	0.213*	0.162	0.073	0.221*	0.023	−0.023
Lt T theta	−0.328**	−0.316**	−0.228*	−0.151	−0.238*	−0.206*	−0.193*
Rt T theta	−0.308**	−0.267**	−0.251**	−0.110	−0.237*	−0.212*	−0.183
Lt T beta 2	0.154	0.252**	0.284**	0.150	0.206*	0.097	0.138
Rt T beta 2	0.190*	0.251**	0.252**	0.094	0.179	0.032	0.054
Lt PO delta	−0.107	−0.148	−0.017	−0.120	−0.150	−0.022	−0.038
Rt PO delta	−0.094	−0.098	−0.053	−0.082	−0.114	−0.005	−0.094
Lt PO theta	−0.341**	−0.343**	−0.254**	−0.184*	−0.258**	−0.200*	−0.184*
Rt PO theta	−0.355**	−0.344**	−0.300**	−0.158	−0.281**	−0.210*	−0.191*
Lt PO alpha	0.272**	0.327**	0.174	0.145	0.238*	0.129	0.123
Rt PO alpha	0.268**	0.294**	0.232*	0.119	0.234*	0.117	0.170

Abbreviations: Lt, left; Rt, right; F, frontal region, T; temporal region, PO; parieto-occipital region.
* Significant difference ($p < 0.05$).
** Significant difference ($p < 0.01$).

4. Discussion

In this study, we investigated the relationship between EEG spectral power and domain-specific cognitive function in HC, aMCI, and AD subjects. Theta and delta band powers tended to increase in selected scalp regions as cognitive impairment progressed, whereas alpha and beta 2 band powers showed a decreasing tendency. Spectral powers with an increasing or decreasing pattern correlated with subcategories of the neuropsychological tests. A summary of results is provided in Table 4.

4.1. Slowing of EEG rhythms in MCI and AD

Differences in spectral power among subjects were most prominent for the theta band, followed by the beta 2 and alpha bands. Spectral power differences in the delta band were less prominent. Slowing of rhythms has been replicated in previous studies on AD patients (Babiloni et al., 2006a,b,c,e, 2004, 2007; Brunovsky et al., 2003; Jelic et al., 2000, 1997; Jeong, 2004; Oishi et al., 2007; Pucci et al., 1998; Rossini et al., 2006; van der Hiele et al., 2007b). The earliest changes in patients with AD are an increase in theta power and a decrease in beta power, followed by a decrease in alpha power. Delta power is known to increase during the later stages of AD. In other words, patients with mild dementia show an increase in theta power and a decrease in beta power, whereas patients with advanced dementia show a decrease in alpha power and an increase in delta power (Coben et al., 1985; Jelic et al., 2000; Jeong, 2004; Rossini et al., 2006). These findings are in line with the results of our study, in which we evaluated patients with aMCI and patients with very mild (CDR 0.5) to mild (CDR 1) AD.

As for the reason of EEG slowing, previous studies have suggested disruption of information processing in the cholinergic system, which contributed to the cognitive impairment in AD (Jeong, 2004). Since acetylcholine projecting from the basal forebrain maintains the desynchronization of EEG activity (Metherate et al., 1992; Spehlmann and Norcross, 1982), cholinergic deficits in AD are believed to be the cause of cortical network disruption, which leads to a slowing of EEG rhythms (Jeong, 2004).

4.2. Regional specific changes in spectral power

In the present study, differences in delta, theta, and alpha band powers were prominent in the posterior scalp regions, including the temporo–parieto-occipital regions, whereas differences in beta 2 band power were prominent in the anterior part, including the fronto-temporal regions. The laterality of spectral powers was not prominent among the three study groups, even during the correlation analyses with the neuropsychological test scores. Prominent changes of spectral power in the temporo-parietal and frontal scalp area in this study accord well with the pathologic and functional image findings of AD. Based on the Braak and Braak staging of AD, neurofibrillary tangles begin to accumulate in the trans-entorhinal and entorhinal cortices and then encroach on the temporo-parietal and frontal association cortices (Braak and Braak, 1991). Functional image studies using [18F]fluoro-2-deoxy-D-glucose PET also revealed reduced metabolism in the temporo-parietal and frontal areas in patients with AD (Alexander et al., 2002). Thus, the neurodegeneration and glucose hypometabolism in the temporo-parietal and frontal lobes are possibly related with the QEEG slowing in those areas.

Integration between the QEEG and default mode network of the resting state functional MRI (fMRI) is drawing attention, since both of them suggest oscillatory connection between the frontal and temporo-parietal regions. The alpha and beta bands or the theta band are known to be associated with the default mode network in the resting state brain (Chen et al., 2008). Recent studies that evaluated the correlation between the QEEG and blood oxygen level dependence (BOLD) signals of fMRI demonstrated a relationship between the alpha to beta band oscillations and BOLD signals and an inverse relationship between theta band oscillation and BOLD signals (Laufs, 2008; Raichle et al., 2001; Scheeringa et al., 2008). In this study, alpha and beta band spectral powers decreased, whereas theta band spectral power increased as the severity of disease increased. We suggest that the decrease in the theta band in the posterior brain (temporo-parietal area) and the increase in the beta 2 band in the anterior brain (fronto-temporal area) in the HC group are possibly associated with the default mode network which would be disrupted in the AD group.

The spectral power of occipital alpha was higher than the spectral powers of other brain regions, in this study. In adults, alpha wave is the dominant background rhythm during the waking state, mainly in the occipital area (Chen et al., 2008). The occipital lobe is, at the same time, one of the least vulnerable areas to AD pathology. Therefore, we considered that a reduction of alpha power in the occipital area might be highlighted in aMCI and AD patients by the high baseline alpha band powers of HC subjects rather than by the reduction of powers caused by the pathologic burden of AD (Osipova et al., 2005).

4.3. Relationship between spectral powers and neuropsychological tests results

Theta, alpha, and beta 2 powers were found to be significantly correlated with memory function. These findings imply that the most meaningful changes developed preferentially in theta, alpha, and beta 2 bands, in the earlier stages of AD (Coben et al., 1985; Jelic et al., 2000; Jeong, 2004; Rossini et al., 2006). The lack of correlation between delta frequency and neuropsychological test results may be due to the mild disease status of the AD patients recruited in this study. Previous QEEG studies that used cognitive tasks revealed an increase in alpha and beta bands with memory performance, including registration, recall, and recognition (Klimesch et al., 2006; Palva and Palva, 2007). Therefore, a decrease of EEG alpha and beta 2 powers from HC to AD, which parallels cognitive deterioration, may also be an evidence of a characteristic oscillation of EEG rhythms in AD. However, the theta band, which is also known to oscillate according to memory tasks (Sauseng et al., 2010), was increased in aMCI and AD patients in the present study. We thought that global increases in theta band spectral power in

Table 4
A Summary of the procedures and results.

	Spectral power
ROIs representing increasing or decreasing pattern	**Control < aMCI < AD**
	Delta: PO (Lt), PO (Rt) Theta: T (Lt), T (Rt), PO (Lt), PO (Rt)
	AD < aMCI < control
	Alpha: PO (Lt), PO (Rt) Beta 2: F (Lt), F (Rt), T (Lt), T (Rt)
Neuropsychological tests with significant correlation ($p < 0.01$)	**Word List Memory:** positively with alpha (PO); negatively with theta (T and PO) **Word List Recall:** positively with beta 2 (T) and alpha (PO); negatively with theta (T and PO) **Word List Recognition:** positively with beta 2 (T); negatively with theta (T (Rt) and PO) **Constructional Recall:** negatively with theta (PO)

Abbreviations: ROIs: regions of interest; aMCI, amnestic mild cognitive impairment; AD, Alzheimer's disease; Lt, left; Rt, right; F, frontal region, T; temporal region, PO; parieto-occipital region.

aMCI and AD patients may have obscured the characteristic theta band oscillation related to memory functioning.

Correlations between the spectral powers and the neuropsychological tests were mainly observed across groups rather than within a group, which supports the consecutive changes in spectral powers according to disease severity. The opposite direction of correlation analyses results between language function test and alpha and delta band spectral powers within the HC group may be attributed to the characteristic changes of the alpha and delta power during resting state (Chen et al., 2008). Since the delta power increased during resting state with eye opening, it may positively correlate with Verbal Fluency test in the HC group. While parieto-occipital alpha power may negatively correlate with language function, since it decreases during resting state with eye opening (Chen et al., 2008).

Targeting a relative spectral power instead of an absolute spectral power could be a limitation of this study. Due to the inter-individual variability of the absolute spectral powers, we divided those values with the summation of the whole absolute spectral power values obtained from all frequency bands in each subject. In this way, we tried to attenuate the inter-individual variability with less influence on the absolute spectral power value (Nuwer, 1988). However, this method may have dissipated the real changes of spectral powers of each frequency band, since it may cause artifactual change in spectral power by changes in other absolute spectral power even though the absolute value remains constant. Thus, relative power estimation in this study may have obscured the real changes occurring in absolute spectral powers.

In summary, we investigated the correlation between QEEG and neuropsychological test results in HC, aMCI, and AD subjects. A linear trend was observed between domain-specific cognitive functioning and theta, alpha, and beta 2 band spectral powers. Regional oscillatory characteristics of EEG reflecting cognitive function suggest that QEEG findings may be a helpful biomarker for differentiating HC, aMCI, and AD.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.clinph.2011.03.023.

References

Alexander GE, Chen K, Pietrini P, Rapoport SI, Reiman EM. Longitudinal PET evaluation of cerebral metabolic decline in dementia: a potential outcome measure in Alzheimer's disease treatment studies. Am J Psychiatry 2002;159:738–45.

Babiloni C, Benussi L, Binetti G, Cassetta E, Dal Forno G, Del Percio C, et al. Apolipoprotein E and alpha brain rhythms in mild cognitive impairment: a multicentric electroencephalogram study. Ann Neurol 2006a;59:323–34.

Babiloni C, Binetti G, Cassarino A, Dal Forno G, Del Percio C, Ferreri F, et al. Sources of cortical rhythms in adults during physiological aging: a multicentric EEG study. Hum Brain Mapp 2006b;27:162–72.

Babiloni C, Binetti G, Cassetta E, Cerboneschi D, Dal Forno G, Del Percio C, et al. Mapping distributed sources of cortical rhythms in mild Alzheimer's disease. A multicentric EEG study. Neuroimage 2004;22:57–67.

Babiloni C, Binetti G, Cassetta E, Dal Forno G, Del Percio C, Ferreri F, et al. Sources of cortical rhythms change as a function of cognitive impairment in pathological aging: a multicenter study. Clin Neurophysiol 2006c;117:252–68.

Babiloni C, Cassetta E, Binetti G, Tombini M, Del Percio C, Ferreri F, et al. Resting EEG sources correlate with attentional span in mild cognitive impairment and Alzheimer's disease. Eur J Neurosci 2007;25:3742–57.

Babiloni C, Cassetta E, Dal Forno G, Del Percio C, Ferreri F, Ferri R, et al. Donepezil effects on sources of cortical rhythms in mild Alzheimer's disease: responders vs. non-responders. Neuroimage 2006d;31:1650–65.

Babiloni C, Frisoni G, Steriade M, Bresciani L, Binetti G, Del Percio C, et al. Frontal white matter volume and delta EEG sources negatively correlate in awake subjects with mild cognitive impairment and Alzheimer's disease. Clin Neurophysiol 2006e;117:1113–29.

Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. Lancet 2006;368:387–403.

Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 1991;82:239–59.

Breslau J, Starr A, Sicotte N, Higa J, Buchsbaum MS. Topographic EEG changes with normal aging and SDAT. Electroencephalogr Clin Neurophysiol 1989;72:281–9.

Brunovsky M, Matousek M, Edman A, Cervena K, Krajca V. Objective assessment of the degree of dementia by means of EEG. Neuropsychobiology 2003;48:19–26.

Chen AC, Feng W, Zhao H, Yin Y, Wang P. EEG default mode network in the human brain: spectral regional field powers. Neuroimage 2008;41:561–74.

Coben LA, Danziger W, Storandt M. A longitudinal EEG study of mild senile dementia of Alzheimer type: changes at 1 year and at 2.5 years. Electroencephalogr Clin Neurophysiol 1985;61:101–12.

Cummings JL. Alzheimer's disease. N Engl J Med 2004;351:56–67.

Duffy FH, Albert MS, McAnulty G. Brain electrical activity in patients with presenile and senile dementia of the Alzheimer type. Ann Neurol 1984;16:439–48.

Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, et al. Mild cognitive impairment. Lancet 2006;367:1262–70.

Gianotti LR, Kunig G, Lehmann D, Faber PL, Pascual-Marqui RD, Kochi K, et al. Correlation between disease severity and brain electric LORETA tomography in Alzheimer's disease. Clin Neurophysiol 2007;118:186–96.

Han C, Jo SA, Kim NH, Jo I, Park MH. Study design and methods of the Ansan Geriatric Study (AGE study). BMC Neurol 2009;9:10.

Huang C, Wahlund L, Dierks T, Julin P, Winblad B, Jelic V. Discrimination of Alzheimer's disease and mild cognitive impairment by equivalent EEG sources: a cross-sectional and longitudinal study. Clin Neurophysiol 2000;111:1961–7.

Jelic V, Johansson SE, Almkvist O, Shigeta M, Julin P, Nordberg A, et al. Quantitative electroencephalography in mild cognitive impairment: longitudinal changes and possible prediction of Alzheimer's disease. Neurobiol Aging 2000;21:533–40.

Jelic V, Julin P, Shigeta M, Nordberg A, Lannfelt L, Winblad B, et al. Apolipoprotein E epsilon4 allele decreases functional connectivity in Alzheimer's disease as measured by EEG coherence. J Neurol Neurosurg Psychiatry 1997;63:59–65.

Jeong J. EEG dynamics in patients with Alzheimer's disease. Clin Neurophysiol 2004;115:1490–505.

Jung KY, Kang JK, Kim JH, Im CH, Kim KH, Jung HK. Spatiotemporospectral characteristics of scalp ictal EEG in mesial temporal lobe epilepsy with hippocampal sclerosis. Brain Res 2009;1287:206–19.

Kelley BJ, Petersen RC. Alzheimer's disease and mild cognitive impairment. Neurol Clin 2007;25:577–609.

Klimesch W, Doppelmayr M, Hanslmayr S. Upper alpha ERD and absolute power: their meaning for memory performance. Prog Brain Res 2006;159:151–65.

Laufs H. Endogenous brain oscillations and related networks detected by surface EEG-combined fMRI. Hum Brain Mapp 2008;29:762–9.

Lee JH, Lee KU, Lee DY, Kim KW, Jhoo JH, Kim JH, et al. Development of the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet (CERAD-K): clinical and neuropsychological assessment batteries. J Gerontol B Psychol Sci Soc Sci 2002;57:P47–53.

Lindau M, Jelic V, Johansson SE, Andersen C, Wahlund LO, Almkvist O. Quantitative EEG abnormalities and cognitive dysfunctions in frontotemporal dementia and Alzheimer's disease. Dement Geriatr Cogn Disord 2003;15:106–14.

Luckhaus C, Grass-Kapanke B, Blaeser I, Ihl R, Supprian T, Winterer G, et al. Quantitative EEG in progressing vs stable mild cognitive impairment (MCI): results of a 1-year follow-up study. Int J Geriatr Psychiatry 2008;23:1148–55.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS–ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–44.

Metherate R, Cox CL, Ashe JH. Cellular bases of neocortical activation: modulation of neural oscillations by the nucleus basalis and endogenous acetylcholine. J Neurosci 1992;12:4701–11.

Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43:2412–4.

Morris JC, Heyman A, Mohs RC, Hughes JP, van Belle G, Fillenbaum G, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology 1989;39:1159–65.

Nuwer MR. Quantitative EEG: I. Techniques and problems of frequency analysis and topographic mapping. J Clin Neurophysiol 1988;5:1–43.

Oishi N, Mima T, Ishii K, Bushara KO, Hiraoka T, Ueki Y, et al. Neural correlates of regional EEG power change. Neuroimage 2007;36:1301–12.

Osipova D, Ahveninen J, Jensen O, Ylikoski A, Pekkonen E. Altered generation of spontaneous oscillations in Alzheimer's disease. Neuroimage 2005;27:835–41.

Palva S, Palva JM. New vistas for alpha-frequency band oscillations. Trends Neurosci 2007;30:150–8.
Perrin RJ, Fagan AM, Holtzman DM. Multimodal techniques for diagnosis and prognosis of Alzheimer's disease. Nature 2009;461:916–22.
Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–8.
Pucci E, Cacchio G, Angeloni R, Belardinelli N, Nolfe G, Signorino M, et al. EEG spectral analysis in Alzheimer's disease and different degenerative dementias. Arch Gerontol Geriatr 1998;26:283–97.
Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci USA 2001;98:676–82.
Reisberg B, Ferris SH, de Leon MJ, Crook T. The global deterioration scale for assessment of primary degenerative dementia. Am J Psychiatry 1982;139:1136–9.
Rossini PM, Del Percio C, Pasqualetti P, Cassetta E, Binetti G, Dal Forno G, et al. Conversion from mild cognitive impairment to Alzheimer's disease is predicted by sources and coherence of brain electroencephalography rhythms. Neuroscience 2006;143:793–803.
Sauseng P, Griesmayr B, Freunberger R, Klimesch W. Control mechanisms in working memory: a possible function of EEG theta oscillations. Neurosci Biobehav Rev 2010;34:1015–22.
Scheeringa R, Bastiaansen MC, Petersson KM, Oostenveld R, Norris DG, Hagoort P. Frontal theta EEG activity correlates negatively with the default mode network in resting state. Int J Psychophysiol 2008;67:242–51.
Spehlmann R, Norcross K. Cholinergic mechanisms in the production of focal cortical slow waves. Experientia 1982;38:109–11.
Tulsky DS, Ledbetter MF. Updating to the WAIS-III and WMS-III: considerations for research and clinical practice. Psychol Assess 2000;12:253–62.
van der Hiele K, Vein AA, Reijntjes RH, Westendorp RG, Bollen EL, van Buchem MA, et al. EEG correlates in the spectrum of cognitive decline. Clin Neurophysiol 2007a;118:1931–9.
van der Hiele K, Vein AA, van der Welle A, van der Grond J, Westendorp RG, Bollen EL, et al. EEG and MRI correlates of mild cognitive impairment and Alzheimer's disease. Neurobiol Aging 2007b;28:1322–9.
Yum MK, Jung KY, Kang HC, Kim HD, Shon YM, Kang JK, et al. Effect of a ketogenic diet on EEG: analysis of sample entropy. Seizure 2008;17:561–6.