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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