A Promising Method to Distinguish Vascular Dementia From Alzheimer’s Disease With Standardized Low-Resolution Brain Electromagnetic Tomography and Quantitative EEG

Lei Wu¹, Lei Wu², Ying Chen¹, and Jiong Zhou¹

Abstract
In clinical settings, it is difficult to distinguish Alzheimer’s disease (AD) from vascular dementia (VD). The present study summarizes a clinical method to distinguish VD and AD at the early stage of the disorders. This study evaluated the possibility of differentiating 25 VD, 25 AD, and 25 healthy individuals (control, CN) by means of power spectral analysis and standardized low-resolution brain electromagnetic tomography (sLORETA) within alpha 1, alpha 2, beta 1, beta 2, delta, and theta frequency bands. Electroencephalogram (EEG) spectral analysis and sLORETA indicated that higher diffuse delta/theta and lower central/posterior fast frequency bands were present in AD compared with CN. VD showed diffuse increased theta power compared with CN and lower delta than AD. AD also presented diffuse higher theta on spectral analysis and decreased alpha 2 and beta 1 values in central/temporal regions by sLORETA. Mini Mental State Examination (MMSE) scores were significantly associated with frontal alpha 1 sLORETA solutions ($r = 0.91616$, $P < .001$) and relative power ($r = 0.87322$, $P < .01$) in AD, but no correlations were found in VD. In conclusion, EEG spectral and sLORETA together could be a tool to distinguish the different EEG rhythmic activities in AD and VD.

Keywords
Alzheimer’s disease, vascular dementia, EEG spectral analysis, sLORETA, neuropsychology

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Introduction
Aging of the population is becoming a universal phenomenon that results in changes in health profiles, especially for the predominance of chronic diseases. According to Ferri et al., 1 4.6 million new cases with dementia arise every year. If new prevention strategies are not implemented, the number of affected people will exceed 81 million by the year 2040.² AD is the main cause of dementia in elderly people.³ It is characterized by progressive and irreversible cognitive deficits and behavioral alterations that affect memory and learning ability, activities of daily living, and quality of life. In clinical settings, it is difficult to distinguish diseases that cause dementia, such as AD, VD, Lewy body, and frontotemporal dementia (FTD). Differentiating AD from VD has become a hot topic in clinical diagnoses.

VD, the second most common dementia after AD, makes up 10% to 20% of cases of dementia in North America and Europe.⁴ Many structural and functional techniques have been used to identify affected brain regions in AD, VD, and other diseases to help improve diagnostic accuracy. For example, position emission tomography, structural magnetic resonance imaging, voxel-based morphometry have been used in the diagnosis of the dementia-related diseases. Before these techniques came into popular use, an old and less expensive method, EEG, had been used in the study of dementia. EEG has been applied to demented patients with the aim of discriminating healthy subjects from those with various types and severity of cognitive impairment or decline.⁵ EEG is a noninvasive diagnostic method with simple logistics, is inexpensive, and is easily available in the majority of countries. Especially for visual analysis, EEG continues to be used in routine clinical practice, and is commonly used to study dementia.⁶

Advanced methods of EEG analysis have been applied to the study of neural activity sources in 3-dimensional models of the brain and different techniques, known as solutions for the EEG inverse problem, have been proposed.⁷ Low-resolution
brain electromagnetic tomography, or LORETA, which allows 3-dimensional localization of cortical EEG generators both in the time and frequency domains, has been successfully applied to studies on normal and pathological aging.3 Using LORETA, decrease of occipital alpha 1 source in AD was found to be significantly higher with respect to controls and patients with VD, and was significantly correlated with disease severity.9 Furthermore, in AD MMSE showed a significant negative correlation with delta source and a positive correlation with alpha 1 source over temporoparietal cortex.5 Comparing magnetic resonance imaging data with LORETA, a correlation between progressive atrophy of hippocampus and decreased cortical alpha power was found across mild cognitive impairment and AD.10 To our knowledge, there are no studies that have explored EEG changes in AD and VD using LORETA. Nishida et al11 used LORETA to address EEG changes and demonstrated reduced alpha power in FTD compared with an increase of beta power in AD. Caso et al12 also proved that spectral analysis and sLORETA provided complementary information that might help characterize different patterns of EEG oscillatory activity in AD and FTD. We hypothesized that there may be a significant difference between AD and VD patients in slow frequency or in alpha. The aim of the present study is to evaluate the effectiveness of EEG spectral and source analysis (with sLORETA) in differentiating AD, VD, and control individuals.

Materials and Methods

Patients

Twenty-five probable AD patients and VD patients (both including 14 males and 11 females) were recruited from May 2007 to May 2011 at the Department of Neurology. AD was diagnosed by the National Institute of Neurological Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association Work Group.13 VD was diagnosed using the National Institute of Neurological Disorders and Stroke Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN) criteria.14 Furthermore, the same number of healthy individuals (14 males and 11 females), with no history of cognitive impairment and neurologic diseases, were also recruited as the CN.

Exclusion criteria were as follows: liver or kidney insufficiency; frank abnormalities by physical and neurological evaluation or neuropsychological tests; drug therapy; psychotropic drug; specific therapy for dementia; alcohol or coffee before EEG recording.

The study was approved by the Ethics Committee of China Medical University. All participants gave informed consent.

Demographic Data Collection

All individuals in the 3 groups underwent a standard battery of examination, including medical history, informant-based history, physical and neurological examination, routine EEG, and standardized neuropsychological testing. Cognitive impairment was assessed using the MMSE, and dementia severity was assessed by the Clinical Dementia Rating.15 All the basic data are presented in Table 1.

EEG Recordings

EEGs were recorded in the morning during admission to the neurologic ward, as part of initial assessment, before neuropsychological testing and specific therapy, such as acetylcholinesterase inhibitors in AD. Standard EEGs, of about 20 minutes, were acquired in the resting awake condition, under control of vigilance, on a computer-based system from 19 standard 10-20 electrode locations. Data, filtered between 0.53 and 70 Hz, were digitized at 256 Hz and coded on 12 bits. Electrode–skin impedance was set below 5 kohm for each electrode.

EEG Spectral Analysis and Its Analysis With sLORETA

EEG spectra were calculated by fast Fourier transform on each epoch of the selected period, allowing a frequency resolution of 0.5 Hz, tapered by a Hanning window. The mean power spectra were analyzed within 7 frequency bands: delta (1.5-4.0 Hz), theta (4.0-8.0 Hz), alpha 1 (8.0-10.0 Hz), alpha 2 (10.0-12.0 Hz), beta 1 (12.0-18.0 Hz), beta 2 (18.0-20.0 Hz), and beta 3 (20.0-30.0 Hz). The global power spectrum was obtained for each subject as average of spectra of all the individual channels; the frequency within the extended alpha range (7.0-13.0 Hz) showing a power peak in the global power spectrum was the individual alpha frequency.16 For EEG source localization, sLORETA was used. The experiment was performed according to the reports of Caso et al12 in 2012.

Statistical Analysis

One-way analysis of variance and Scheffe’s test for post hoc analysis were performed on demographic data, MMSE scores, and individual alpha frequency. As neuropsychological tests

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Table 1. Demographic Data.

<table>
<thead>
<tr>
<th>Index</th>
<th>CN</th>
<th>VD</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Gender (female/male)</td>
<td>14/11</td>
<td>14/11</td>
<td>14/11</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.4 ± 2.14</td>
<td>64.3 ± 1.73</td>
<td>69.8 ± 3.01</td>
</tr>
<tr>
<td>Education (years)</td>
<td>8.14 ± 0.81</td>
<td>7.95 ± 0.73</td>
<td>7.61 ± 0.39</td>
</tr>
<tr>
<td>Follow-up (years)</td>
<td>—</td>
<td>1.98 ± 0.34</td>
<td>1.95 ± 0.27</td>
</tr>
<tr>
<td>MMSE score</td>
<td>27.9 ± 0.51</td>
<td>23.1 ± 0.68***</td>
<td>22.7 ± 0.38***</td>
</tr>
<tr>
<td>Individual alpha frequency</td>
<td>9.73 ± 0.24</td>
<td>9.51 ± 0.31</td>
<td>8.86 ± 0.28***</td>
</tr>
<tr>
<td>Clinical dementia rating</td>
<td>—</td>
<td>0:38:0</td>
<td>0:38:0</td>
</tr>
</tbody>
</table>

Abbreviations: CN, control; AD, Alzheimer’s disease; VD, vascular dementia; MMSE, Mini Mental State Examination.

* Differences between groups were found for MMSE (1-way analysis of variance: F = 14.25; P < .001; Scheffe’s post hoc analysis: CN vs AD, ***P < .001; CN vs VD, ***P < .001) and for individual alpha frequency (1-way analysis of variance: F = 9.57; P < .01; Scheffe’s post hoc analysis: CN vs AD, ***P < .01).
were not performed on the control group, scores were compared between AD and VD patients using Student’s t test.

Results

Demographic and Basic Data

Demographic data were not significantly different between the CN, VD, and AD groups (Table 1): All patients and subjects were well matched regarding age, gender, and education. Also, the Clinical Dementia Rating showed no significant difference in VD and AD.

EEG Spectral Analysis

Alpha frequency in AD (8.86 Hz) was significantly decreased compared with CN (9.73 Hz) and VD (9.51 Hz) (Table 1; 1-way analysis of variance: \(F = 6.47, P = .006\)), but no significant difference was found between CN and VD.

To reflect the spectral analysis more compactly, the spectral analysis results were obtained by grouping power values into 5 regions of interest; frontal, central, temporal, parietal, and occipital. Figure 1 presents the bar graphs of relative power within 6 frequency bands in the 3 groups and the statistical analysis. The relative power of AD, compared with CN, showed a shift from faster to slower frequencies, including an increase of delta over posterior regions, a widespread increase of theta, a decrease of alpha 1 over all regions and alpha 2 over temporocentral areas. The comparison between VD and AD showed differences within the theta band only: Theta relative power was highly represented in VD over the entire scalp. Compared with VD, AD had higher delta/theta power over posterior regions (Figure 1).

sLORETA Analysis

Normalized sLORETA solutions were also used to identify the differences of sources of delta, theta, alpha 1, alpha 2, and beta 2 rhythms between CN–AD, CN–VD and VD–AD (Figure 2). sLORETA showed that higher delta and theta and lower alpha and beta solutions were found when comparing AD with CN. Increased theta of VD compared with CN was confirmed by higher values of sLORETA solutions, especially over the centroposterior areas. Furthermore, sLORETA showed some significant differences between AD and VD patients: lower delta values and higher alpha 2 and beta 1 values over the posterior regions of VD compared with AD (Figure 2).

Correlation Analysis

To identify the distinguishing function of EEG spectral values, we performed correlation analysis between EEG spectral values and neuropsychological tests. Correlation analysis showed significant difference between patients using all patients’ data as a single group. Especially for AD, MMSE scores were significantly associated with frontal alpha 1 sLORETA solutions.
Figure 2. sRODETA solutions of interested region in alpha 1 (A), alpha 2 (B), beta 1 (C), beta 2 (D), delta (E), and theta (F) band of VD, AD, and CN. Post hoc analysis results are graphically displayed inside the horizontal bar over the graph: *P < .05, **P < .01, and ***P < .001 refer to CN vs AD; #P < .05, ##P < .01, and ###P < .001 refer to VD vs AD; $P < .05, $$$P < .01, and $$$$P < .001 refer to CN vs VD.
Abbreviations: CN, control; AD, Alzheimer’s disease; VD, vascular dementia.

Discussion

We attempted to distinguish probable VD from AD by using the spectral profile of cortical EEG sources and by sLORETA. In clinical settings, the EEG activity and the frequency of abnormal EEG recordings could reflect the severity of dementia. We aimed to evaluate if in an early stage of VD we might find any EEG differences in comparison with mild AD and healthy individuals by using an integrated sLORETA and EEG spectral methods.

For AD, spectral analysis indicated a significant power increase within the delta band in occipital regions and within the theta band over all regions of interest, whereas a significant parietooccipital alpha 1, temporal alpha 2, and widespread beta 1 and beta 2 power decreases were observed, compared with the control group. Furthermore, the VD spectral pattern did not significantly differ from controls except for a widespread increase of theta power, as previously reported. VD, compared with AD, showed a decrease of delta power over posterior regions and of theta power over all regions of interest.

sLORETA results were similar to some previous studies, but these studies mainly compared FTD and AD using classical spectral analysis and sLORETA together. Our study is in line with previous literature about the sLORETA approach to study AD, even if theta band values seem to be more critical in differentiating controls from AD in the very early stage of mild AD. In the present study, both EEG spectral and sLORETA values for alpha rhythm source in AD patients compared with controls were well preserved over the frontal areas.

EEG cortical activity depends on a complex balance among different neurotransmitters systems, within cholinergic pathways. Alpha rhythms are mainly regulated by inhibiting the transmission of sensorimotor and cognitive information among subcortical and cortical pathways. Therefore, the reduction of fast cortical rhythms in mild AD may be related with the impairment of cholinergic pathway resulting in an abnormal increase of cortical excitation or disinhibition during the resting state. Our results indicated that VD patients showed a decrease of alpha band compared with controls and an increase of beta band in comparison with AD. But Nishida et al did not find any significant differences between AD and the FTD group in slow frequency bands or in alpha band when using the same EEG spectral and sLORETA analyses. Perhaps different experiment procedures and conditions caused this discrepancy.

We also attempted to explore any statistically significant correlation between cortical powers, sources of EEG rhythms and
cognitive function. Frontal alpha 1 power correlated positively with MMSE scores, confirmed by both spectral and sLORETA analysis. Actually, the intensity of alpha 1 value changes in pathological aging as a function of the global cognitive level.21

In conclusion, the present study indicated that both classic EEG spectral analysis and EEG source analysis could significantly distinguish between AD, VD, and healthy individuals. EEG spectral analysis and sLORETA analysis together could be a tool to distinguish the EEG rhythmic activities between AD and VD patients.

Declaration of Conflicting Interests
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References