Clinician's Road Map to Wavelet EEG as an Alzheimer's disease Biomarker

Clin EEG Neurosci published online 16 October 2013
DOI: 10.1177/1550059413486272

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What is This?
 Clinician’s Road Map to Wavelet EEG as an Alzheimer’s disease Biomarker

Paulo Afonso Medeiros Kanda1, Lucas R. Trambaiolli2, Ana C. Lorena3, Francisco J. Fraga2, Luis Fernando I. Basile1, Ricardo Nitrini1, and Renato Anghinah1

Abstract

Alzheimer’s disease (AD) is considered the main cause of dementia in Western countries. Consequently, there is a need for an accurate, universal, specific and cost-effective biomarker for early AD diagnosis, to follow disease progression and therapy response. This article describes a new diagnostic approach to quantitative electroencephalogram (QEEG) diagnosis of mild and moderate AD. The data set used in this study was composed of EEG signals recorded from 2 groups: (S1) 74 normal subjects, 33 females and 41 males (mean age 67 years, standard deviation = 8) and (S2) 88 probable AD patients (NINCDS-ADRDA criteria), 55 females and 33 males (mean age 74.7 years, standard deviation = 7.8) with mild to moderate symptoms (DSM-IV-TR). Attention is given to sample size and the use of state of the art open source tools (LetsWave and WEKA) to process the EEG data. This innovative technique consists in associating Morlet wavelet filter with a support vector machine technique. A total of 111 EEG features (attributes) were obtained for 162 probands. The results were accuracy of 92.72% and area under the curve of 0.92 (percentage split test). Most important, comparing a single patient versus the total data set resulted in accuracy of 84.56% (leave-one-patient-out test). Particular emphasis was on clinical diagnosis and feasibility of implementation of this low-cost procedure, because programming knowledge is not required. Consequently, this new method can be useful to support AD diagnosis in resource-limited settings.

Keywords
quantitative EEG (QEEG), Alzheimer’s disease, wavelets, support vector machine (SVM)

Submitted 19 September 2012; accepted 18 March 2013.

Introduction

Alzheimer’s disease is considered the main cause of dementia in Western countries.1,2 Nevertheless, there is no ideal biomarker to define AD, and definitive diagnosis can only be established on autopsy or biopsy.3 Therefore, AD diagnosis should be based on clinical history, laboratory tests, neuroimaging, and neuropsychological batteries. However, these clinical assessments are nonspecific and costly.4 Consequently, there is a need for an accurate, universal, specific, and cost-effective biomarker for early diagnosis, and to follow disease progression and therapy response. QEEG is one of the promising diagnostic tools to improve diagnostic accuracy and identify patterns5-7 in AD. Most of the studies have been carried out on EEG reactivity8 and frequency changes.9,10 The usual AD EEG findings are displacement of background frequency into delta and theta ranges11 and central12 alpha dropout. Usually, the fast Fourier transform (FFT) algorithm is used. Unfortunately, the highly complex dynamics of the AD EEG are difficult to study with this methodology. An additional problem is small sample sizes13,14 usually found in this line of clinical research. A small sample size will skew results, and it is likely that results are due to chance rather than the experiment.

This article describes a new diagnostic approach to QEEG diagnosis of mild and moderate AD. This innovative technique consists of associating Morlet wavelet transform (WT)15 with Library for Support Vector Machines (LIBSVM)16 support vector machine (SVM) technique.17 In this study, an SVM classifier was designed using the Waikato Environment for Knowledge Analysis (WEKA) tool. SVMs offer both algorithmic and computational advantages when compared with artificial neural networks,18 and have already been successfully used for automated AD diagnosis based on spectral peak and coherence parameters.19,20 Particular emphasis is on sample size and the clinical use of state-of-the-art open source tools21 to process the EEG after recording. This low-cost clinical procedure would be feasible for any neurologist to implement in

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resource-limited settings, because programming knowledge is not required. In addition, the use of WT plus LIBSVM classifier improved the efficiency of EEG diagnosis with higher success rates in comparison with previous reported methods.19

Materials and Methods

Patients

The data set used in this study was composed of EEG signals recorded from 2 groups: Subjects 1, 74 normal subjects, 33 females and 41 males (mean age ± standard deviation = 67 ± 8 years). Inclusion criteria for cognitively normal cohort were as follows: Clinical Dementia Rating (CDR)24 score = 0, Brazilian version of the Mini-Mental State Examination (MMSE)25 score ≥26, and no indication of functional cognitive prior to enrollment based on an interview with the subject. Subjects 2, 88 probable AD patients, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association criteria (NINCDS-ADRDA),26 55 females and 33 males (mean age ± standard deviation = 74.7 ± 7.8 years) and mild to moderate symptoms (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, DSM-IV-TR).27 Other inclusion criteria for AD cohort were as follows: CDR score ≥1, MMSE24 score ≤24, and presence of functional and cognitive decline over the previous 12 months, based on detailed interview with a knowledgeable informant. Subjects did not have diabetes mellitus, kidney disease, thyroid disease, alcoholism, liver disease, lung disease, or vitamin B12 deficiency, other known causes of cognitive impairment.

Data Acquisition and Preprocessing: LetsWave Software

EEGs were recorded for 20 minutes while awake, relaxed and eyes closed. Artifact epochs of 40 seconds were selected from each EEG for database inclusion. LetsWave was used for time-frequency analysis with Morlet WT.28,29 It is an open source EEG signal-processing toolbox written in Borland Delphi 7 and running under Microsoft Windows. It was developed to perform fast multivariate analyses of event-related potentials and EEG, with specific focus on time-frequency analysis.21 LetsWave generates a time-frequency representation of each EEG epoch for visual inspection. The Morlet wavelet is defined as the product of a complex exponential wave and a Gaussian envelope.30 Morlet wavelet can be used to analyze time series that contain nonstationary power at many different frequencies.31 As compared with the windowed Fourier transform, which decomposes the signal using a fixed window of analysis, the WT adapts the width of its window of analysis as a function of frequency, and thereby offers an optimal compromise for time-frequency resolution.32 Morlet wavelet was used because it has one of the best time-frequency localization as specified by the Heisenberg’s uncertainty principle.33

Signal Preprocessing

After EEG signal filtering in the wavelet domain, frequency bands were divided into delta (0.5-3.5 Hz), theta (4.0-7.6 Hz), alpha (8.0-13.1 Hz), beta (13.5-30.0 Hz), and full band (0.5-30.0 Hz).34 Then, 11 attributes were extracted from the amplitude in microvolts: maximum, minimum, average, median, standard deviation, variance, interquartile range, coefficient of variation, variance-to-mean ratio, and signal-to-noise ratio. Thus, attributes were extracted for 5 bands in all 20 channels, totaling 1100 attributes of 162 EEGs.

Support Vector Machines

SVMs have been used in many EEG applications,35,36 including in the diagnosis of AD.19,37 SVMs constitute a machine learning technique based on statistical learning theory.28 SVMs separate data by a hyperplane, considering bounds in the generalization ability of a linear classifier.39 Furthermore, they show good generalization performance even in the presence of high numbers of features.40 Accordingly, given a training data set $T$ containing $n$ pairs $(x_i, y_i)$, where $x_i$ is a data point with $m$ dimensions (eg, the features extracted from the EEG exam of a given patient) and $y_i \{ -1; +1 \}$ is the class of $x_i$ (the diagnosis: $-1$ for normal and $+1$ for AD), SVMs seek the linear classifier $g(x) = sgn(w \cdot x + b)$ separating data from classes $+1$ and $-1$ with minimum error while also maximizing the margin of separation between these classes. This is the optimization problem solved in this process:

$$\text{Minimize} : \|w\|^2 + C \sum_{i=1}^{n} \xi_i \tag{1}$$

under the restrictions: $y_i (w \cdot x_i + b) \geq 1 - \xi_i$ and $\xi_i \geq 0$, for $i = 1, \ldots, n$, where $C$ is a constant that imposes a different weight for training error over the generalization of the classifier and $\xi_i$ are slack variables. The restrictions are originally imposed to ensure that no training data should be within the margins of separation between the classes. The slack variables relax these restrictions on the margins in order to avoid an overfitting to training data, and also for dealing with noisy data (Figure 1).

For nonlinear separation of a data set, it is first mapped by a function $\Phi$ to a space of higher dimension (feature space), where the classes become linearly separable. The mathematical tool employed for the computation of $\Phi$ is named kernel. The kernel $K$ is a function that takes 2 variables $x$ and $x_i$ representing 2 data points, and calculates the dot product between them in the feature space. Since all computations involving data points in SVMs are in the form of dot products, the nonlinearization of SVMs can be easily accomplished through the use of a proper kernel function. A summary of the technique used in this article is shown in Figure 2.
WEKA SVMs Induction

WEKA is an open source software issued under the General Public License (GPL). It is a collection of machine learning algorithms for data mining tasks, such as, data preprocessing, classification, regression, clustering, association rules, and visualization. LIBSVM kernel class linear and radial basis function were induced with WEKA, using default parameter values to allow fair comparisons among different features. The default parameters employed were S 0, K 2, D 3, G 0.01, R 0, N 0.5, M 40, C 1, E0.001, and P 0.1. Moreover, WEKA can evaluate the worth of a subset of attributes by considering the individual predictive ability of each feature along with the degree of redundancy between them. Consequently, from each patient data set it was possible to select 172 main features for proband classification.

Results

The descriptive results suggest that the risk of dementia was increased in females and in subjects with low education. The average MMSE score in the control group was 28.4 (standard deviation = 1.49) and in AD patients 17.7 (standard deviation = 3.8; Table 1).

Three data set tests were used in WEKA: leave-one-patient-out, 10-fold cross-validation, and percentage split. Leave-one-out cross-validation signifies that \( n \) is equal to the number of examples (162). In other words, each proband is compared with all the others. It uses the greatest amount of training data from the data set. Having 10 folds means 90% of full data is used for training (and 10% for testing) in each fold test. In percentage split, the classifier is evaluated on how well it predicts a certain percentage of the data that is held out for testing.

WEKA split the original data set obtained from 162 EEG epochs into 66% for training and 33% for testing. The data set distribution in the test set is different from that in the training data. Table 2 shows the classification on 2 different kernel functions: kernel class liblinear and radial basis function (with WEKA targeted projection pursuit filter–TPP). LIBSVM linear showed the best performance with 92.92% accuracy when percentage split was tested. Furthermore, leave-one-patient-out in radial basis function reached 84.56% accuracy. The use of the linear kernel in general leads to simpler models than the radial basis function kernel and should be preferred when both have similar predictive performance.

Data mining is about solving problems by analyzing data and discovering patterns in databases. There are 2 extremes for the expression of a pattern: as a black box whose innards are effectively incomprehensible, and as a transparent box whose construction reveals the structure of the pattern. Both are able to make good predictions. This data set was constituted by 1100 features × 162 probands = 178 200 features (attributes). Consequently, it was assumed a black box model, and the results were achieved without the requirement of knowing the features. Nevertheless, WEKA has an attribute evaluator that shows the main features used in group classification (Table 3).

Discussion

We face a global epidemic of AD as the world’s population ages. Today, in America, someone develops AD every 68 seconds. By 2050, AD prevalence is projected to be 11 to 16 million. In 2012, payments for health care, long-term care, and hospice services for people aged ≥65 years with AD and other dementias are expected to be $200 billion. Similarly, the prospects of an ageing society in developing countries are...
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surprising. For instance, Brazil was 16th, in the world ranking, in 1950 with 2.1 million elderly people; by 2025 it has been estimated that it will rank sixth with a staggering 31.8 million people older than 60 years, the largest proportional increase in the world over this period. In 75 years, the Brazilian elderly population will have increased 15 times, whereas the population as a whole will increase only 5-fold51 with a prevalence of dementia in the elderly (\(\geq 65\) years) of approximately 7.1%. 1

Consequently, an urgent need exists to develop an efficient low-cost screening tool for clinicians to diagnose AD. In this article, there was an association between low educational level and a higher prevalence of dementia as many previous investigations have suggested.52,53 Moreover, the prevalence of AD in women is in agreement with previous reports. 1,53,54 Furthermore, the results suggest group differences in delta and theta band features (Table 3). These findings are in accordance with medical literature on the subject.55,56 However, this was an age-matched controls study to avoid EEG bias. Consequently, there should be no age differences between groups.

EEG, though of high relevance in cognitive investigation, poses a number of technical challenges because it is clearly stochastic and nonstationary.57 Neither the use of wavelets58,59 nor SVM is new in EEG.17,60,61 In recent decades, wavelet analysis (WA) has grown quickly in comparison with FFT. WA can be used to analyze nonlinear and nonstationary time series signals such as EEG.52 WA can discriminate frequency and signal amplitude better than FFT.63 On the contrary, FFT cannot identify abrupt changes in time and frequency, which are characteristics of cerebral oscillations.64 There are lower resolution and “leakage” effects in the FFT algorithm.65,66 Therefore, some authors have postulated that WA is better than FFT for EEG analysis.63,67

For example, Petrosian et al14 suggested that trained recurrent neural networks, combined with wavelet preprocessing, may be useful to discriminate between EEGs of patients with mild AD and age-matched control subjects. Wan et al68 investigated a larger EEG sample. This Daubechies WT study was carried out on 103 AD patients and 124 age-matched normal elderly controls. The authors decomposed recorded EEG signals into frequency sub-bands and analyzed EEG spectral changes. Polikar et al69 tried a new effort by using multiresolution analysis of ERPs and wavelets. The differential diagnosis between AD and controls had sensitivity of 73.5% and specificity of 79.20%. Lehmann et al20 studied 161 probands using SVM and neural networks. They reached values of 89% and 88% for sensitivity and specificity, classifying AD versus controls. Ahmadlou and Adeli58 developed a wavelet-chaos methodology as a potential AD marker with a sensitivity of 100% and a specificity of 97.8%. Table 4 shows a summary of the main articles in the field.

### Table 1. Descriptive Differences Between Groups.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Alzheimer’s Disease</th>
<th>Difference</th>
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<tbody>
<tr>
<td>Total N = 162</td>
<td>74</td>
<td>88</td>
<td>14</td>
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<tr>
<td>Education (mean years)</td>
<td>9.5</td>
<td>5.3</td>
<td>(P &lt; .0001^a)</td>
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<tr>
<td>Gender (female)</td>
<td>33/74</td>
<td>55/88</td>
<td>(P = .02^a)</td>
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<tr>
<td>Mini-Mental State Examination (mean)</td>
<td>28</td>
<td>17</td>
<td>(P &lt; .0001^a)</td>
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<tr>
<td>Age (mean years)</td>
<td>67.16</td>
<td>74.78</td>
<td>(P = .76^b)</td>
</tr>
</tbody>
</table>

\(^{a}\)T test.
\(^{b}\)F test.

### Table 2. Classification on 2 Different Kernel Functions: Kernel Class Liblinear and Radial Basis Function.\(^a\)

<table>
<thead>
<tr>
<th>LibSVM Kernel</th>
<th>Method</th>
<th>Accuracy (%)</th>
<th>(\kappa)</th>
<th>TP AD</th>
<th>TP Control</th>
<th>Precision AD</th>
<th>Precision Controls</th>
<th>AUC</th>
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<tr>
<td>Radial basis</td>
<td>66%</td>
<td>89.09</td>
<td>0.77</td>
<td>0.96</td>
<td>0.80</td>
<td>0.85</td>
<td>0.95</td>
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<td></td>
<td>10-fold</td>
<td>83.95</td>
<td>0.67</td>
<td>0.9</td>
<td>0.75</td>
<td>0.81</td>
<td>0.87</td>
<td>0.83</td>
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<td></td>
<td>leav1out</td>
<td>84.56</td>
<td>0.68</td>
<td>0.9</td>
<td>0.77</td>
<td>0.82</td>
<td>0.87</td>
<td>0.84</td>
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<tr>
<td>Linear</td>
<td>66%</td>
<td>92.72</td>
<td>0.85</td>
<td>0.96</td>
<td>0.88</td>
<td>0.90</td>
<td>0.95</td>
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<td></td>
<td>10-fold</td>
<td>82</td>
<td>0.64</td>
<td>0.78</td>
<td>0.86</td>
<td>0.87</td>
<td>0.77</td>
<td>0.82</td>
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<tr>
<td></td>
<td>leav1out</td>
<td>80.86</td>
<td>0.61</td>
<td>0.81</td>
<td>0.79</td>
<td>0.82</td>
<td>0.78</td>
<td>0.80</td>
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Abbreviations: SVM, support vector machine; TP, true positive; AD, Alzheimer’s disease; AUC, area under the curve; 66%, percentage split; 10-fold, 10-fold cross-validation; leav1out, leave one patient out.

\(^a\)Accuracy refers to the LibSVM ability to discriminate whether one individual is normal or AD. The kappa statistic (\(\kappa\)) measures the agreement of prediction with the true class (1.0 signifies complete agreement). The TP\(^{51}\) rate is the proportion of examples that were classified as class x, which truly have class x. Precision is the proportion of the examples that truly have class x among all those that were classified as class x. Area under the curve\(^{46}\) of a receiver operating characteristic (ROC) is a measure of how well attributes can distinguish between controls and AD.\(^{41}\)

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Table 3. Features (Attributes) Used in SVM Classification of AD Versus Controls.a

| | Fp1 | Fp2 | Fz | F7 | F8 | F3 | F4 | Fz | T3 | T4 | C3 | C4 | CZ | T5 | T6 | P3 | P4 | PZ | O1 | O2 | Oz |
| Delta | Maximum | Minimum | Average | Median | Standard deviation | Variance | Interquartile range | Range | Coefficient of variation | Variance-to-mean ratio | Signal-to-noise ratio |
| Theta | Maximum | Minimum | Average | Median | Standard deviation | Variance | Interquartile range | Range | Coefficient of variation | Variance-to-mean ratio | Signal-to-noise ratio |
| Alpha | Maximum | Minimum | Average | Median | Standard deviation | Variance | Interquartile range | Range | Coefficient of variation | Variance-to-mean ratio | Signal-to-noise ratio |

(continued)
Table 3. (continued)

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Abbreviations: SVM, support vector machine; AD, Alzheimer's disease.

*Delta was the more important band. Top row, electrodes; first column, bands; second column, features.
recently, Trambaioli et al\textsuperscript{71} and Falk et al\textsuperscript{72} developed a new preprocessing scheme, using spectrotemporal amplitude modulation analysis, and applied it to the same data, obtaining an accuracy of 90.6\% with 90.5\% sensitivity.

The novelty of the present article relies on the optimization of a post-processing method to filter and analyze EEG data with free open source software. In addition, it is feasible for any neurologist to implement in resource-limited settings. This method is low cost and easy to perform by clinicians, providing that the EEG can be exported to ASCII file (Let’sWave compatible). Also, this effort constitutes one of the largest studies of its kind to date. A sample of 162 patients was tested to diagnose AD and it obtained accuracy of 92.72\%, precision of 0.9 and area under the curve of receiver operating characteristic of 0.92.

Most important, comparing a single patient versus the total data set resulted in an accuracy of 84.56\%. Usually, it is not difficult to group individuals with the same diagnoses and find EEG similarities among them. However, it is more challenging to select a patient, and compare him or her with a given group. The leave-one-patient-out test accomplished this. Consequently, it would be possible to use this methodology, in a resource-limited community health clinic in developing countries.

These results set this study apart from similar earlier results. As a matter of fact, a Pubmed search in September 2012 confirms the relevance and uniqueness of this article. The search terms and setting analysis, and applied it to the same data, obtaining an accuracy of 90.6\% with 90.5\% sensitivity.

The novelty of the present article relies on the optimization of a post-processing method to filter and analyze EEG data with free open source software. In addition, it is feasible for any neurologist to implement in resource-limited settings. This method is low cost and easy to perform by clinicians, providing that the EEG can be exported to ASCII file (Let’sWave compatible). Also, this effort constitutes one of the largest studies of its kind to date. A sample of 162 patients was tested to diagnose AD and it obtained accuracy of 92.72\%, precision of 0.9 and area under the curve of receiver operating characteristic of 0.92.

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These results set this study apart from similar earlier results. As a matter of fact, a Pubmed search in September 2012 confirms the relevance and uniqueness of this article. The search terms and results are as follows: Alzheimer’s + EEG + machine learning techniques, 16 articles; Alzheimer’s + EEG + wavelets, 5 articles; Alzheimer’s + EEG + svm, 3 articles; Alzheimer’s + EEG + machine learning techniques + wavelets, 3 articles; and Alzheimer’s + EEG + wavelets + svm, 0 articles. It is important to realize that this methodology is not intended to replace other diagnostic approaches but to complement them. Further studies in this laboratory should address questions such as the use of this method with mild cognitive impairment and with other dementia groups.

**Conclusion**

This article extends previous work on trial-by-trial AD diagnosis.\textsuperscript{19} AD EEG features were investigated for 162 probands. After EEG recording, free open source software was used for WT and SVM processing. The results obtained with percentage split were accuracy of 92.72\% and area under the curve of 0.92. Leave-one-patient-out reached accuracy of 84.56\% and area under the curve of 0.84. Particular emphasis was on diagnosis and feasibility of implementation in a community health clinic setting, because programming knowledge is not required. These findings suggest that this method can provide support for the diagnosis of AD. This work waits for replication.

**Declaration of Conflicting Interests**

The author(s) declared no conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The author(s) received no financial support for the research, authorship, and/or publication of this article.

**References**


63. Feng ZY. Analysis of rat electroencephalogram during slow wave sleep and transition sleep using wavelet transform. *Sheng Wu Hua Xue Yu Sheng Wu Wu Li Xue Bao (Shanghai)*. 2003;35:741-746.