

RESEARCH ARTICLE

Interval-based features of auditory ERPs for diagnosis of early Alzheimer's disease

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Abstract

Introduction: It has been demonstrated that event-related potentials (ERPs) mirror the neurodegenerative process of Alzheimer's disease (AD) and may therefore qualify as diagnostic markers. The aim of this study was to explore the potential of interval-based features as possible ERP biomarkers for early detection of AD patients.

Methods: The current results are based on 7-channel ERP recordings of 95 healthy controls (HCs) and 75 subjects with mild AD acquired during a three-stimulus auditory oddball task. To evaluate interval-based features as diagnostic biomarkers in AD, two classifiers were applied to the selected features to distinguish AD and healthy control ERPs: RBFNN (radial basis function neural network) and MLP (multilayer perceptron).

Results: Using extracted features and a radial basis function neural network, a high overall diagnostic accuracy of 98.3% was achieved.

Discussion: Our findings demonstrate the great promise for scalp ERP and interval-based features as non-invasive, objective, and low-cost biomarkers for early AD detection.

KEYWORDS

Alzheimer's disease, artificial neural network, event-related potential, interval-based features, multilayer perceptron, radial basis function neural network

1 | INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with a gradual decline in episodic memory, attentional processes, and cognitive functions.¹ Although AD can be diagnosed at an advanced stage of the disease with high diagnostic accuracy, as there are no obvious symptoms at the beginning of the disease, early diagnosis of AD remains a major challenge for clinicians and researchers.² In fact, the neurophysiological basis for the cognitive and behavioral dysfunction in AD is not fully understood³ and a definitive diagnosis can only be made by *post mortem* autopsy or, while alive, a brain biopsy.⁴ Although

there is no cure for AD, early diagnosis via accurate, inexpensive, and non-invasive diagnostic techniques would allow for better care and thus improve the quality of life for AD patients, their families, and caregivers.⁵

The earliest stage of AD diagnosis often involves neuropsychological tests and evaluations of the patient's history.⁶ For symptomatic individuals, diagnosis is supported by biomarkers derived from cerebrospinal fluid (CSF)⁷ and neuroimaging techniques such as magnetic resonance imaging (MRI),⁸ positron emission tomography (PET),⁹ computed tomography (CT), diffusion tensor imaging (DTI),¹⁰ and single photon emission computed tomography (SPECT).¹¹ Unfortunately,

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physicians are often deterred from ordering these diagnostic methods routinely because of their costs and lack of accessibility in a primary care setting.¹²

More recent research efforts have explored the development of more convenient and non-invasive means, including the use of scalp electroencephalography (EEG), which is a non-invasive, well-tolerated, and economical electrophysiological tool.^{1,13} Fortunately, EEG-based biomarkers can be used to identify neuronal deterioration and decay in synapses caused by AD progression because EEG signals have their origin in the underlying activity of the cerebral cortex.¹⁴ In this regard, investigated characteristics include EEG slowing (a reduction in power at low frequencies as well as an increase at high frequencies),¹⁵ reduced coherence,¹⁶ reduced complexity,¹¹ and chaoticity.¹⁷

Event-related potentials (ERPs) of EEG signals comprise a set of components that can be discriminated according to their latency (milliseconds), polarity (positive/negative), amplitude (μV), and scalp distribution.¹⁸ It has been demonstrated that cognitive ERPs of EEG signals, which have been widely used to study dementia, can predict the pathology of AD years prior to clinical diagnosis.¹⁹ In this respect, some researchers have investigated ERPs in patients with AD and studied group differences between AD and healthy controls (HC) and several features of the ERP have been proposed as biomarkers in AD.

The P300 component, for instance, the most prominent and most extensively studied component, is elicited by auditory, visual, or somatosensory stimuli, and has been associated with various cognitive processes such as attention, working memory, and executive function.²⁰ Numerous ERP studies have reported a significant increase in latency for P300,^{18,21–24} suggesting that measures of P300 latency can reliably distinguish between AD patients and HCs. Moreover, some studies have also demonstrated lower P300 amplitude for AD patients compared to HCs.^{21,25} However, there remains a lack of agreement regarding the amplitude of P300.²⁶

In addition, N200, considered an index of automatic cognitive processes, is usually investigated along with the P300 component and is provoked by a novel infrequent stimulus during an oddball paradigm.²⁷ Having investigated this ERP component, a number of studies reported longer latency^{22–25,28} and a decrease in amplitude²⁸ of N200 in AD.

Furthermore, early ERPs, N100 and P200, represent the sensory process and are associated with attention.²⁹ While the dominant view is that early ERP components are mostly unaffected by AD, and thus not ideal biomarkers,³⁰ a few studies have found prolonged N100 and P200 latencies^{21,22} and reduced N100 and P200 amplitudes^{21,28} among AD patients compared to healthy individuals.

In an effort to develop a diagnostic procedure that discriminates between AD and age-matched control individuals, Jimenez-Rodriguez et al.³¹ proposed two novel measures of complexity of the shape in time series: spectral matching complexity (SMC) and spectral matching entropy (SSME). Performing a linear discriminant classification with only complexity measures, they achieved a sensibility of 81% and a specificity of 85%. Kim et al.³² achieved the recognition rate of 81.9% for the untrained dataset after computing EEG and ERP statistical and nonlinear features as well as spectral features and by feeding them to

RESEARCH IN CONTEXT

1. Systematic review: It has been demonstrated that event-related potentials (ERP) can predict the pathology of Alzheimer's disease (AD) years prior to clinical diagnosis. While ERP components have been widely investigated in numerous studies, feature selection and classification techniques have received less attention.
2. Interpretation: A dementia classification framework based on ERP data has been developed and implemented. Interval-based features were extracted from cognitive ERP recordings of brain electrical activity and different methods of feature selection and two classifiers were used to distinguish AD patients and healthy controls. Our results clearly show that extracted features could detect AD at an early stage with remarkable accuracy.
3. Future directions: Further analyses should extend the proposed algorithm to multi-class situations such as the classification of mild cognitive impairment (MCI), mixed AD, vascular dementia, and healthy controls.

an artificial neural network (ANN). By multiresolution analysis of ERPs, Polikar et al.³³ achieved an average ensemble performance of 72.4% and best ensemble performance of 75%, with sensitivity of 68.6% and specificity of 69.2%.

The objective of this study was to assess the viability of an automated classification approach. We used interval-based features³⁴ extracted from cognitive ERP recordings of brain electrical activity during an oddball paradigm to distinguish AD patients from HCs. Different methods of feature selection were used and then two classifiers (radial basis function neural network [RBFNN] and multilayer perceptron [MLP]) were applied to the selected features to distinguish AD patients and HCs.

2 | METHODS

2.1 | DATABASE

Data were extracted from the open source Neuronetrix clinical database and consist of 99 mild AD patients (age: 76.2 ± 0.74) diagnosed according to National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association criteria and 100 age-matched HCs (age: 73.2 ± 0.71). However, the final sample includes 75 AD individuals and 95 HCs due to missing data of some tones in some subjects. Owing to the experiment requirement, all of the participants had adequate visual and auditory acuity to allow neuropsychological and ERP testing.

The average Clinical Dementia Rating (CDR) and Mini-Mental State Examination (MMSE) scores for the AD patients were 0.9 ± 0.03

and 23.4 ± 0.19 , respectively, and the MMSE score for the normal subjects was 29.1 ± 0.08 . The mean number of educational years was 14.9 ± 0.29 years for the HCs, and 14.4 ± 0.32 years for AD patients.

In addition to a diagnosis of AD, an MMSE score between 21 and 26; a CDR score of 0.5, 1, or 2; and delayed-recall scores on the Wechsler Logical Memory II subscale of less than or equal to 3 for 0 to 7 years of education, less than or equal to 5 for 8 to 15 years of education, and less than or equal to 9 for 16 or more years of education were the required inclusion criteria for recruiting subjects with mild AD. HCs had an MMSE score of 27 or higher, a CDR score of 0, and delayed-recall scores on the Wechsler Logical Memory subscale of equal to or higher than 4 for 0 to 7 years of education, equal to or higher than 6 for 8 to 15 years of education, and equal to or higher than 10 for 16 or more years of education.²⁸ The exclusion criteria were the use of antidepressant medication except selective serotonin reuptake inhibitor, or evidence of other neurological or psychiatric disorders. Hachinski Ischemic Score and Geriatric Depression Scale Short Form scores were less than or equal to 4 and less than or equal to 5, respectively. Finally, all subjects were requested to withhold sedatives and dietary memory supplements for the 72 hours prior to testing.²⁸

ERP data were collected through a three-stimulus oddball paradigm. Electrical brain activities were recorded from seven electrode sites (Fz, Cz, Pz, F3, P3, F4, and P4) according to the international 10/20 standards using a COGNISION Headset (Neuronetrix). Electrodes were referenced to averaged mastoids (M1, M2), and Fpz served as the common electrode. The skin contact impedance was below 70 k Ω . Recording was initiated at ≈ 240 ms before stimulation and maintained for ≈ 944 ms thereafter, digitized at 125 Hz, and bandpass filtered from 0.3 to 35 Hz.²⁸

Subjects were seated comfortably in a chair in an office under normal lighting conditions. Between 300 and 400 stimuli were binaurally presented through insert earphones at 70 dB volume in pseudo-randomized order within a three-stimulus oddball paradigm so that target and distractor tones were never presented sequentially. The standard stimulus was the 1000 Hz tone (75% probability), the target stimulus was the 2000 Hz tone (15% probability), and unexpected distractor stimulus was white noise (10% probability). The tone duration for each stimulus was 100 ms with rise and fall times of 10 ms and the interstimulus interval varied from 1.5 to 2 s. Subjects were instructed to press a button using their dominant hand in response to each target tone. Trial averaging and extraction of ERP measures were automatically performed by the COGNISION system software (Neuronetrix).²⁸

2.2 | Feature extraction

Previous studies demonstrated excellent classification accuracy on several different datasets using interval-based features derived from ERP signals over time segments of various lengths.^{34–36} Kuncheva and Rodriguez³⁴ examined four traditionally used feature extraction meth-

ods (principal component analysis, independent component analysis, autoregression, and wavelets) as well as the interval feature extraction method on two visual ERP datasets and showed that the top accuracies with the interval features were often larger than those with the other feature extraction methods, and in many experimental configurations, those differences were statistically significant.

Considering only intervals of size power of two, for each ERP, time series spanned 149 time points; the lengths of time intervals would be 2, 4, 8, 16, 32, 64, and 128. Overall a set of 796 time intervals was achieved (for reviews, see Kuncheva and Rodriguez³⁴). For each interval, the average amplitude of the point set, the standard deviation, and the covariance with the time variable were calculated. Adding the 149 original features to this collection, we extracted 2537 features ($3 \times 796 + 149$) from the ERP signals. Computations were performed using the platform MATLAB R2013a, and data of each electrode and stimulus were processed separately.

2.3 | Feature selection

Due to the possible scattering of input values of the neural network, the network may be unable to achieve a desirable outcome. Thus, through normalizing the data, the input values were limited to a certain range. Features are normalized by equation (1), which brings all values into the range [0, 1].

$$X' = \frac{X - X_{min}}{X_{max} - X_{min}} \quad (1)$$

where X_{min} and X_{max} are the minimum and maximum values of original features in each dimension.

It has been generally recognized that high-dimensional input data in classifiers typically increase computational complexity and computing time. This often leads to bias and overfitting in classification when limited data are available.³⁷ For the purpose of classifying, feature selection is adopted to select the optimal features in this study.

Different feature selection methods were performed to eliminate redundant features used for training classification models. This allowed us to alleviate the effect of the curse of dimensionality, speed up the learning process, and improve the model's performance. To this end, the Feature Selection Library (FSLib) MATLAB Toolbox was used to rank and select a subset of relevant features based on their degree of relevance, performance, or importance. Forty relevant features were selected as the input vector of the RBFNN and MLP classifiers because they yielded better results. An equal number of features feeding to the classifiers also enabled us to have a fair comparison between them.

In this study, we tested different methods of feature selection, including infinite feature selection (Inf-FS),³⁸ relief feature selection (Relief-F),³⁹ feature selection via concave minimization (FSV),^{40,41} mutual information feature selection (Mutinfo),⁴² support vector machine recursive feature elimination (SVM-RFE),⁴³ Fisher's,⁴⁴

multi-cluster feature selection (MCFS),⁴⁵ and feature selection via eigenvector centrality (EC-FS).⁴⁶ Regarding classification, FSV and SVM-RFE outperformed other feature selection methods.

2.4 | Classification

To classify the ERP data into HC and AD groups, two classifiers were adopted: RBFNN and MLP. RBFNNs have been widely used in the last decade as a powerful tool in modeling and simulation, because they are proven to be universal approximators of nonlinear input-output relationships with any complexity.⁴⁷ The MLP neural network classifier is the most commonly used neural-network architecture because it enjoys properties such as the ability to learn and generalize, fast operation, and ease of implementation. One major characteristic of these networks is their ability to find nonlinear surfaces separating the underlying patterns.⁴⁸

Cross-validation, which is a robust validation method, was used in this study to evaluate the classification performance and to reduce bias. The data from 150 subjects were initially divided into 10 folds. One of the folds was for the testing and the other nine folds were used for training the proposed models. This procedure was repeated 10 times until each fold had been used for testing. Ten times 10-fold cross-validation was carried out for each classifier model, which gives 100 testing accuracy, sensitivity, and specificity, from which averages were calculated. Averaging results over several iterations would lower the fluctuation and provide statistically meaningful results.⁴⁹ Classification accuracy is defined as the percentage of correctly identified subjects over the total number of subjects in the dataset. Classification sensitivity is defined as the probability of a positive diagnosis given that the patient does in fact have the condition. Specificity is defined as the probability of a negative diagnosis given that the patient does not have the disease.³³

3 | RESULTS

Presenting results for each combination of feature selection methods and classifiers would not be pragmatic and would unnecessarily extend the length of this article; hence, best results are provided here. The average classification results for all electrodes and three stimuli obtained using FSV and SVM-RFE as feature selection methods and the two classifiers are presented in Tables 1, 2, and 3. It is noticeable that the classification algorithms achieved high average classification accuracy of > 75.1% for RBFNN and of > 79.2% for MLP. Accuracy ranges from 75.1% to 96.1%. For RBFNN, the classification accuracy was from 75.1% to 89.7% while for MLP, the accuracy ranged from 79.2% to 96.1%.

Comparing the results of standard tone presented in Table 1 with other electrodes, we can see that the classifiers had a better performance at Pz and P3 electrodes. The best results were achieved from the Pz electrode using MLP classifier and FSV feature selection method (with an accuracy of 93.2%, a sensitivity of 91.6%, and a specificity of 94.2%). Results for the target tone are presented in Table 2. The best results were obtained at F3 electrode using MLP classifier and SVM-RFE feature selection method (with an accuracy of 93.4%, a sensitivity of 89.8%, and a specificity of 96.0%). The results for distractor tone are reported in Table 3. Comparing results of seven electrodes, the classifiers generally yielded better results at F3 electrode with the best results using MLP classifier and SVM-RFE feature selection method (with an accuracy of 96.1%, a sensitivity of 95.6%, and a specificity of 96.4%).

To assess the overall performances of classifiers we combined all the features (i.e., 2537 features \times 7 electrodes \times 3 stimuli = 53,277 features) and the top 40 features were used in the classification models. The overall results are given in Table 4. It can be observed from Table 4 that RBFNN classifier and SVM-RFE feature selection method achieved the highest average classification accuracy, of 98.3%.

TABLE 1 The results of classifiers for standard tone for seven electrodes

Classifier/feature selection method	Classifier results (%)	Fz	Cz	Pz	F3	P3	F4	P4
RBFNN/FSV	Accuracy	79.7	85.2	87.6	82.7	86.6	80.2	83.5
	Sensitivity	78.3	86.7	88.8	81.5	87.0	78.1	82.6
	Specificity	80.2	84.4	86.9	84.6	86.1	82.4	85.0
RBFNN/SVM-RFE	Accuracy	80.1	88.2	88.4	82.4	86.7	85.3	85.7
	Sensitivity	81.3	89.2	92.6	81.0	85.5	84.2	87.2
	Specificity	78.9	88.0	84.9	83.4	88.2	86.0	84.1
MLP/FSV	Accuracy	83.9	87.8	93.2	84.4	89.2	81.4	88.8
	Sensitivity	81.0	84.3	91.6	81.5	85.5	75.2	87.6
	Specificity	87.1	90.3	94.2	87.3	92.1	86.3	90.2
MLP/SVM-RFE	Accuracy	87.9	89.8	92.4	80.2	91.5	85.5	89.1
	Sensitivity	85.3	87.0	90.8	77.9	87.6	81.5	88.8
	Specificity	89.4	91.6	93.6	81.9	95.2	89.2	89.2

Abbreviations: FSV, feature selection via concave minimization; MLP, multilayer perceptron; RBFNN, radial basis function neural network; SVM-RFE, support vector machine recursive feature elimination.

TABLE 2 The results of classifiers for target tone for seven electrodes

Classifier/feature selection method	Classifier results (%)	Fz	Cz	Pz	F3	P3	F4	P4
RBFNN/FSV	Accuracy	83.8	86.4	75.1	79.9	82.3	82.8	78.8
	Sensitivity	83.4	86.7	73.8	74.3	79.4	82.5	73.8
	Specificity	84.5	86.3	76.4	84.5	85.1	83.7	83.5
RBFNN/SVM-RFE	Accuracy	83.6	85.3	79.8	82.8	86.4	84.4	86.2
	Sensitivity	80.8	80.0	76.4	78.5	84.8	80.1	84.8
	Specificity	85.5	89.3	83.6	86.3	88.1	88.0	87.2
MLP/FSV	Accuracy	90.8	88.6	80.1	84.1	85.9	86.7	79.2
	Sensitivity	86.9	88.0	76.9	79.5	82.1	82.6	71.8
	Specificity	93.8	88.9	82.9	88.6	89.2	90.0	84.9
MLP/SVM-RFE	Accuracy	90.0	87.5	84.6	93.4	85.6	89.9	89.7
	Sensitivity	87.3	84.0	80.0	89.8	82.1	86.4	86.5
	Specificity	91.9	91.2	89.4	96.0	88.0	93.0	92.9

Abbreviations: FSV, feature selection via concave minimization; MLP, multilayer perceptron; RBFNN, radial basis function neural network; SVM-RFE, support vector machine recursive feature elimination.

TABLE 3 The results of classifiers for distractor tone for seven electrodes

Classifier/feature selection method	Classifier results (%)	Fz	Cz	Pz	F3	P3	F4	P4
RBFNN/FSV	Accuracy	85.1	83.5	82.8	88.4	82.1	86.8	79.1
	Sensitivity	84.7	80.8	80.8	89.2	80.2	85.2	78.2
	Specificity	85.5	86.2	84.0	87.4	83.0	88.2	80.0
RBFNN/SVM-RFE	Accuracy	85.8	89.7	87.3	86.9	77.6	85.2	81.6
	Sensitivity	86.4	86.1	83.9	85.9	79.7	86.4	78.5
	Specificity	86.2	92.4	89.7	88.2	76.1	84.5	85.2
MLP/FSV	Accuracy	92.2	87.8	90.0	92.9	85.4	88.9	84.9
	Sensitivity	90.7	83.5	86.5	93.3	81.4	87.8	83.5
	Specificity	93.4	91.1	93.2	93.2	88.7	90.7	86.0
MLP/SVM-RFE	Accuracy	91.5	89.4	92.7	96.1	83.7	88.5	93.1
	Sensitivity	88.2	86.2	89.3	95.6	82.1	89.1	92.0
	Specificity	93.9	92.7	95.0	96.4	85.5	88.1	93.8

Abbreviations: FSV, feature selection via concave minimization; MLP, multilayer perceptron; RBFNN, radial basis function neural network; SVM-RFE, support vector machine recursive feature elimination.

TABLE 4 The overall performances of classifiers

Classifier/feature selection method	Classifier accuracy (%)	Classifier sensitivity (%)	Classifier specificity (%)
RBFNN/FSV	97.4	99.5	95.9
RBFNN/SVM-RFE	98.3	97.2	99.4
MLP/FSV	97.8	98.4	97.5
MLP/SVM-RFE	98.1	97.6	98.4

Abbreviations: FSV, feature selection via concave minimization; MLP, multilayer perceptron; RBFNN, radial basis function neural network; SVM-RFE, support vector machine recursive feature elimination.

4 | DISCUSSION

AD is the most prevalent form of dementia accompanied by progressive memory loss, cognition loss, and functional decline. As the diversity of dementia symptoms does not allow for easy diagnosis, the search for an accurate biological marker for early diagnosis of the disease remains an open challenge. Because controlling disease progression is much more effective in the preliminary stages, early diagnostic methods and biomarkers that could reveal the disease at the earliest onset of it, prior to the manifestation of clinical symptoms, are sought. To this end, this study was concerned with automated early diagnosis of AD, using a non-invasive, objective, and low-cost biomarker that could be measured in a community clinic, where most patients get their first intervention.

Regarding dementia, ERPs have been used in numerous studies, most of which have exploited ERP components when studying AD. Nonetheless, feature selection and classification techniques have received less attention. In this research, a dementia classification framework based on ERP data has been developed and implemented in the MATLAB R2013a environment to classify subjects with AD from HCs. To meet our objective, interval-based features of ERPs recorded during a three-stimulus oddball paradigm were explored as potential biomarkers for discriminating AD patients from HCs. The results for the two-class discrimination are encouraging as an overall accuracy of 98.3% was achieved using the RBFNN classifier and SVM-RFE feature selection method.

Among previous studies that have explored various ERP features for the discrimination of AD from normal individuals, Jimenez-Rodriguez et al.³¹ extracted SMC and SSME features and reached a sensibility of 81% and a specificity of 85%. Kim et al.,³² by computing statistical, non-linear, and spectral features of EEG and ERP and feeding them to ANN achieved a recognition rate of 81.9%. Compared to other similar studies in EEG, we have also been able to achieve satisfactory results. For instance, McBride et al.¹³ extracted complexity and regional spectral features of EEG and obtained an accuracy of 85.4% and Falk et al.,⁵⁰ analyzing EEG amplitude modulation, achieved an accuracy of 90.6%, a sensitivity of 90.5%, and a specificity of 90.9%.

The findings of this work clearly show that adopting an interval-based feature extraction method and the exploitation of artificial neural networks is practical and this method could detect AD at an early stage with a remarkable accuracy. In addition, the results of this study parallel the previous findings³⁴ and support the idea that the interval-based feature extraction method could be implemented to produce comparable results in various classification scenarios during different tasks. It is also expected that this technique could be applied to automatically diagnose other neurological and psychiatric disorders such as mild cognitive impairment (MCI), attention deficit hyperactivity disorder, and autism spectrum disorder. It is noteworthy that to distinguish between AD and HC subjects, patients with mild AD have been used which is one of the special advantages of this research. In addition, the exclusion of patients suffering from severe psychiatric disorders and avoiding sedatives and/or memory dietary supplements are other benefits of this study as these types of disorders and medications could

directly impact patterns of brain signals. Another advantage of our method is its non-invasive characteristic and its independence of cultural and educational influence; therefore, there is no limit to such tests. Moreover, its procedure is totally free from radiation exposure, and easy to operate.

One limitation of this study, however, is that we have focused on a two-class classification problem (AD vs. HC), and did not evaluate patients suffering from other types of dementia; hence, we cannot comment on whether these findings would differentiate AD from other causes of cognitive impairment, such as MCI.

To improve this methodology and conduct more precise examinations, it is suggested that MCI subjects be included in future studies. Future studies should also take sex into consideration, as sex differences may also play a role. It is also thought that by combining more robust and complex classifiers and other feature extraction techniques the diagnostic accuracy of the method may increase. Future research is expected to extend the proposed algorithm to multi-class situations such as the classification of MCI, mixed AD, vascular dementia, and HC. They should also cover various brain disorders other than dementia to perform multi-class dataset classification to separate normal brain function from various neurological disorders.

In summary, the results of our AD classifiers, with the best overall accuracy of 98.3%, further confirm the usefulness of the ERP data as a complementary approach in evaluating cognitive disorders.

CONFLICTS OF INTEREST

The authors report no conflicts of interest.

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