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Electrophysiological Biomarkers

Temporospatial components of brain ERPs as biomarkers for Alzheimer's disease

Robert M. Chapman[a,*], Margaret N. Gardner[a], Rafael Klorman[b], Mark Mapstone[c], Anton P. Porsteinsson[d], Inga M. Antonsdottir[a], Lily Kamalyan[a]

[a]*Department of Brain and Cognitive Sciences and Center for Visual Science at the University of Rochester, Rochester, NY, USA*
[b]*Department of Clinical and Social Sciences in Psychology at the University of Rochester, Rochester, NY, USA*
[c]*Department of Neurology, University of California Irvine, Irvine, CA, USA*
[d]*Department of Psychiatry, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA*

Abstract

Introduction: Developing biomarkers that distinguish individuals with Alzheimer's disease (AD) from those with normal cognition remains a crucial goal for improving the health of older adults. We investigated adding brain spatial information to temporal event-related potentials (ERPs) to increase AD identification accuracy over temporal ERPs alone.
Methods: With two-step principal components analysis, we applied multivariate analyses that incorporated temporal and spatial ERP information from a cognitive task. Discriminant analysis used temporospatial ERP scores to classify participants as belonging to either the AD or healthy control group.
Results: Temporospatial ERPs produced a cross-validated area under the curve of 0.84. Adding spatial information through a formal procedure significantly improves classification accuracy.
Discussion: A weighted combination of temporospatial ERP markers performs well in detecting AD. Because ERPs are noninvasive and inexpensive, they may be promising biomarkers for AD that can add functional information to other biomarker systems while providing the individual's probability of correct classification.

Keywords: Discriminant analysis; Brain event-related potentials (ERP); Electrophysiology; Alzheimer's disease (AD); Aging; Principal components analysis (PCA); Receiver-operating characteristic (ROC); Posterior probabilities; Two-step PCA; Temporospatial ERPs; Diagnosis; Brain spatial information; Temporal ERP components

1. Introduction

Alzheimer's disease (AD) is a persistent degenerative neurological disorder with primary cognitive deficits in the memory domain and whose impact is rising drastically [1]. Definitive diagnosis of AD was only possible postmortem until recent advances in the design and refinement of biomarkers. These biomarkers, which are typically based on the molecular and neuroanatomic pathology of AD, have had a major impact on the clinical assessment of AD in living patients [2]. However, functionally these markers do not adequately differentiate between the effects of normal aging and the degeneration seen in AD. This nonspecificity is further compounded by the fact that there is no biomarker that reliably and robustly correlates with actual clinical, cognitive decline in AD.

Cognitive brain event-related potentials (ERPs) have been shown to detect AD in individuals [3]. Along with behavioral methods, ERPs can give precise neurophysiological bases for cognitive processes, including perception and memory, which are adversely affected in AD [4,5]. In both clinical and research settings, ERPs offer higher temporal resolution compared to other brain imaging methods in that they can detect electrophysiological changes

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*Corresponding author. Tel.: +(585) 275-8679; Fax: +(585) 271-3043.
E-mail address: rmc@cvs.rochester.edu

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accurately in milliseconds. However, ERP biomarkers are often developed without a formal, mathematical method of combining temporal and spatial information. Adding spatial information to temporal ERP measures may increase their ability to identify AD. There are few systematic ways to combine temporal and spatial properties without arbitrary assumptions. ERPs are by nature multivariate measures [6]; therefore, simplistic measuring tools may not suffice to incorporate the richness of information about the temporal properties of an ERP waveform and its distribution over the scalp. New statistical approaches that build upon previous work [7–10] effectively combine temporal and spatial brain ERP properties formally and mathematically, but these approaches have not yet been applied to the development of biomarkers for AD where reducing the number of possible predictors while encompassing their most salient information is key. In addition, because ERPs are inexpensive and noninvasive to participants, improving their utility as a clinical tool to assess functional changes related to AD is of great interest.

This study investigates if the multivariate addition of brain spatial information to temporal ERP components improves classification of early-stage AD by building upon previous work that identified individuals with AD using a single electrode [3]. We gathered data from participants with early-stage AD and cognitively normal older adults using a cognitive/perceptual paradigm known to elicit ERPs representative of the cognitive processes typically affected by AD. We then identified clinically usable ERP measures for AD by applying multivariate analyses that incorporated both temporal and spatial information into useful composite measures. These temporospatial ERP measures perform well in a cross-validated discriminant analysis with a receiver-operating characteristic (ROC) area under the curve (AUC) of 0.84 and may represent a step toward establishing ERPs as functional measures of cognitive decline that can potentially enhance other biomarkers.

2. Methods

2.1. Study participants

We studied 36 elderly individuals diagnosed with early-stage AD and 36 like-aged healthy controls (Table 1). These 72 participants were recruited from the Memory Disorders Clinic at the University of Rochester and other affiliated clinics. All AD participants were evaluated by memory-disorder physicians and met established clinical criteria for AD (National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association, NINCDS-ADRDA) [1] and DSM-4 TR (Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision) criteria for Dementia of the Alzheimer's Type [12] and were considered early in the course of the disease (see Supplementary Table 1). The memory disorders physicians, who were blind to our ERP study data, based their assessments on patient history, relevant laboratory findings, neuropsychological testing, and imaging studies routinely performed as part of a comprehensive clinical assessment of dementia. Healthy control participants were cognitively normal for their age and demographically similar to the AD participants (Supplementary Table 1). Most healthy control participants were selected from the Memory Disorders Clinic and underwent the same clinical assessment for cognitive impairment. Some healthy control participants were volunteers from the community and were evaluated with a comprehensive neuropsychological test battery designed to assess memory impairment.

Table 1
Demographic and behavioral results for healthy control and early-stage AD groups with *t*-tests for significant differences between groups

Characteristics	Alzheimer's disease	Healthy control	*P*-value
Age	74.9 (7.4)	74.2 (7.1)	NS
Education	14.4 (2.9)	15.5 (2.4)	NS
MMSE*	24.6 (2.7)	29.1 (0.9)	<0.01
% Correct on ERP task†	91.2 (15.7)	99.0 (1.8)	<0.0001

Abbreviations: AD, Alzheimer's disease; ERP, event-related potential.

NOTE. Values appear as mean (SD) unless otherwise indicated. The age and education information is in number of years. AD and healthy control groups each contained 18 women and 18 men, totaling 36 participants.

*MMSE = Mini-Mental State Examination [11] (maximum of 30 points, where higher scores indicate greater cognitive functioning). Neuropsychological test results are in Supplementary 1.

†Number of correctly answered trials divided by the total number of trials (204) in our number-letter paradigm (median [interquartile range]). Only correct trials were used in subsequent ERP analyses.

There were no significant group (AD and healthy control) or gender differences for age and education (Table 1). Thirty-four of the 36 participants in the AD group were taking cholinesterase inhibitors to treat mild AD (one man and one woman were not). All elderly participants had a clinically administered score of 19 or higher on the MMSE [11] (AD group mean = 24.6). Exclusion criteria for all elderly groups included clinical (or imaging) evidence of stroke, Parkinson's disease, HIV/AIDS, and reversible dementias, as well as treatment with benzodiazepines, antipsychotic, or antiepileptic medications. Our study was conducted under IRB approval from the University of Rochester Research Subjects Review Board, and informed consent was obtained from each participant.

2.1.1. Neuropsychological assessment

Each participant was administered a comprehensive neuropsychological test battery (Supplementary Table 1, has 29 scores) to assess cognitive processes impacted in AD and memory disorders. As expected, the healthy control group typically performed significantly better than the AD group did. Of note, the Geriatric Depression Scale [13] did not differ significantly between the groups, and no scores were indicative of active depression. Also, the two groups did not differ significantly on the American version of the Adult National Reading Test (AMNART) [14], suggesting comparable levels of verbal intelligence. Because our AD group was generally early in the course of the disease, there was

no significant difference on the Blessed Dementia Scale [15,16] that assesses functional capacity.

2.2. The number-letter paradigm

In our number-letter task [3,17,18], the intratrial stimulus sequence contains two single-digit numbers (randomly selected from 1 to 6) and two letters (randomly selected from A to F) with these four stimuli flashed in random order at fixed 750-ms intervals (intratrial parts). On a number-relevant block of trials, the participant compared the two numbers in each trial for numerical order, the letters being irrelevant to the task. On a letter-relevant block of trials, the participant compared the two letters in each trial for alphabetic order, and the numbers were irrelevant to the task. Importantly, memory storage of the first relevant stimulus, which randomly appeared in intratrial part 1 or 2, was required to compare it with the second relevant stimulus, which randomly appeared in part 3 or 4. For more information, see the Supplementary Materials and Supplementary Fig. 1.

The number-letter task permits examination of ERPs in response to 16 varying task conditions: two task relevancies (relevant, irrelevant), two stimulus types (letters, numbers), and four intratrial stimulus times (called intratrial parts).

2.3. Participant performance on the number-letter task

All participants were capable of performing the number-letter task (on average both groups had greater than 90% accuracy [Table 1]). The healthy control group significantly outperformed the AD group (medians of 99.0% and 91.2% correct, $F[1,70] = 39.30, P < .0001$). There was no main effect of gender or group by gender interaction on number-letter task performance. Using behavioral task performance alone as a predictor of dementia produced a sensitivity of only 0.58.

2.4. EEG recording

Scalp electrodes (a subset of the 10/20 electrodes including O1, O2, OZ, T3, T4, T5, T6, P3, P4, PZ, C3, C4, CZ, F3, F4, and left outer canthus for electrooculogram (EOG) with reference to linked earlobes) were used to non-invasively record electrical brain activity while the participant performed the number-letter task. The EOG detected blinks and eye movements (see the Supplementary Materials for more information). Mean artifact rejection rate for the healthy control group was 10.5% (SD = 19.2) and for the AD group was 8.6% (SD = 13.6). There was no significant difference in artifact rejection rate [$t(70) = -0.49$, $P = .62$].

2.5. Event-related potential components: Temporospatial principal components analysis

We derived ERPs for each participant from his/her electroencephalogram (EEG) vectors (155 time points per electrode for each stimulus) by averaging each vector separately for each of the 16 task conditions in this experimental design (plus the two blanks—see the Supplementary Materials) and for each of the 16 electrodes. The topography of average ERP waveforms for each group for relevant and irrelevant task conditions appears in Supplementary Fig. 2.

Because the ERP itself is a multivariate observation (due to its many post-stimulus time samples), we applied Varimax Principal Components Analysis (PCA) [6,19–21] to identify and develop operational measures of the ERP components. Volume conduction in the brain suggests an additive ERP model, which underlies the PCA process in extracting the component structure [6]. PCA can be used to separate functionally distinct events by forming weighted linear combinations of the original measurements that capture most of the relevant variance. Temporospatial PCA can be useful when it is likely components overlap both in space and in time. It also achieves a great deal of data reduction and removes the need to preselect time zones of interest or particular electrodes or scalp zones to study. Temporospatial PCA is a two-step procedure [8].

We first submitted to a Varimaxed temporal PCA the ERP data from the two groups of 36 AD and healthy control participants (described in Section 2.1) and data from an additional group of 36 participants clinically diagnosed with mild cognitive impairment (MCI) (see Supplementary Materials for demographics and further discussion of these additional participants, including their ERP waveforms). We included this set of 36 MCI participants to solve for ERP components that would be more generalizable to a wider array of individuals [22,23] with varying cognitive and memory capabilities. The component scores from these MCI participants are not used in further analysis here.

The data matrix that entered the temporal PCA contained 155 variables (time points per epoch) and 31,104 cases (108 participants × 16 electrodes × [two task relevancy × two stimulus types × four intratrial parts] + two blanks). This PCA was computed using a correlation matrix [24]. In the temporal PCA, there were nine ERP temporal components that accounted for 98% of the total variance (each component accounted for > 0.5% of the variance itself). One component represented an ocular-related artifact [25] that is not discussed further.

To compute spatial factors in the second PCA step, we submitted the component scores from the first step for each individual and each experimental condition (relevancy, intratrial part) for each of the eight temporal ERP components. This was done by transforming the data so that the electrode sites (which also have component scores because they were scored during the temporal step) became the variables and all the participants, conditions, and temporal components became the observations in the input matrix of this second step. After Promax rotation, this process yielded spatial factors. For each temporal component, there were two spatial factors whose Eigenvalues were greater than 1. In general, these two

factors accounted for between 59% and 79% of the total variance and had an interfactor correlation between 0 and 0.07 (Supplementary Table 2).

2.6. Discriminant analysis

The temporospatial ERP scores were retained for discriminant analysis [26,27] to build a discriminant function with weights that classifies participants as belonging to either the AD or the healthy control group. The linear discriminant function is composed of the sum of the selected component scores, each weighted by their contribution in differentiating the participant groups. Once the variables are selected, linear discriminant functions, which include appropriate weights for each variable, can be computed and applied to each individual in the data set. We performed a development set, where each of the 72 participants contributed to the creation of the discriminant function. To test the reliability of our discriminant functions, a jackknifed cross-validation was also performed. In this analysis (commonly called a one-left-out validation), unique discriminant functions were built for each individual without using his or her data in any step of computing the PCA steps in finding the factor structure and discriminant analyses (choosing predictors and calculating discriminant coefficients). These functions were then applied to that omitted participant. This procedure is done for each participant in the set. Because the participant being classified does not contribute to the development of the function that is applied to that participant, this method achieves a "nearly unbiased estimate" [26]. See the Supplementary Materials for more information on how this analysis was conducted.

Discriminant analysis also provides the posterior probabilities of group membership for each individual [3,28,29]. These were analyzed to determine the confidence in each individual's classification. None of the subjects in either the AD or healthy control groups was a multivariate outlier.

3. Results

The temporospatial components extracted from PCA (Fig. 1) included well-known components, such as P3 [17,30–33], Contingent Negative Variation (CNV) [34], C250 [24,31,35,36], and other short- and long-latency components.

Spatial factors for each temporal factor are also shown in Fig. 1. Each temporal factor had two spatial factors: one loading on mostly anterior electrode sites and the other on posterior sites. We found no spatial factors with striking laterality differences for any of the temporal components.

The temporospatial PCA produced component scores for each spatial factor for each temporal component. These scores were further differentiated by the experimental conditions: Relevancy (relevant, irrelevant) and intratrial part (1–4). This led to a possible 128 temporospatial component scores (eight experimental conditions × two Spatial Factors × eight temporal components) per subject (case). While temporospatial PCA performed a great deal of data reduction by extracting the most important dimensions in the data set, we selected potential variables for the discriminant analysis by choosing spatial factors and experimental conditions to encompass a wide variety of data. Our aim was to reduce the number of variables a priori to a ratio of approximately six cases to one variable for the discriminant process. In our selection process, which was guided by previous work [3,24], we made certain each temporal component was represented at least once as we have found that the weighted combination of multiple temporal ERP components is best for discriminating between groups. Because each temporal component is orthogonal to each other, the information each contributes to the discriminant analysis is likely to be fairly independent.

After our selection, we submitted 13 temporospatial ERP scores to a stepwise discriminant procedure to further reduce the number of predictors based on the correlational and covariant relationships among the set of predictors. It selected 11 scores as discriminators between the AD and healthy control groups (Table 2). These included relatively short-latency components (such as C200, C115, and C250) and longer-latency components (such as C525, P3, and CNV). In addition, both anterior and posterior spatial factors were chosen.

3.1. Discriminant analysis

The SAS DISCRIM procedure was used to calculate discriminant coefficients for each predictor. Given the linear discriminant functions it developed (Table 2), we applied these sets of weighted predictors to each participant for classification as a member of the AD or healthy control group. Note that the weights included positive and negative values. The accuracy of these classifications was judged against the gold standard, blinded independent clinical assessment (described more thoroughly in the Methods). We first applied the functions to the data used to develop them (the development set) and calculated sensitivity (the capacity of the test to detect AD in the population) and specificity (the extent to which the test is specific to AD). We also produced ROC curves and determined the AUC, which can be considered the probability of a correct classification (Fig. 2). Using our temporospatial ERP measures, our development set produced an excellent classification success ($\chi^2 = 40.53$, $P < .0001$) with an AUC of 0.93, sensitivity of 0.88, and specificity of 0.86. The jackknifed cross-validation (Fig. 2) also performed well ($\chi^2 = 20.20$, $P < .0001$), with AUC = 0.84, sensitivity = 0.81, and specificity = 0.72.

3.2. Posterior probabilities

Fig. 3 illustrates an example of using the posterior probabilities to provide a quantitative context to the binary

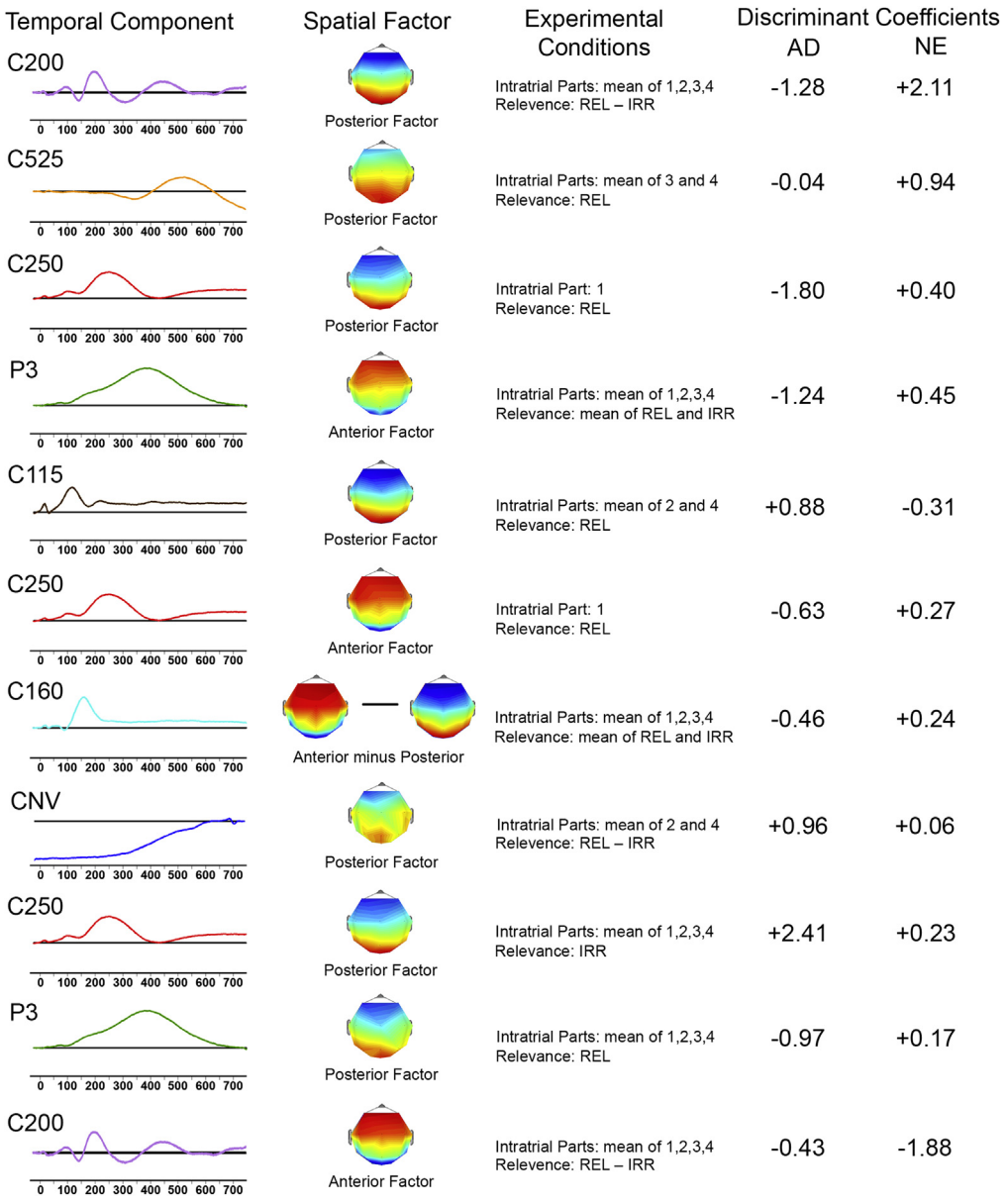

Fig. 1. ERP temporospatial components. Each of the seven ERP temporal components on the left are named either with its common designation (e.g., P3) or based on maximum poststimulus (ms) (e.g., C250). For easier interpretability, these waveforms have the metric restored (by multiplying the vector of component loadings with the vector of standard deviations at each time point and given a component score of 1 [6]). There were two spatial factors for each temporal component: one distributed more anterior and one over posterior scalp locations; these topo maps show ERP temporospatial factor loadings. Red hues indicate more positive factor loadings. Blue hues indicate more negative factor loadings. Abbreviation: ERP, event-related potential.

diagnostic decision for each individual. We ordered each participant by the probability of belonging to the AD group as determined by our temporospatial ERP measures. Participants extremely likely to be in the healthy control group (C) had nearly 0% chance of being classified as AD; conversely, participants extremely likely to be in the AD group (A) had nearly 100% chance of being in the AD group. Participants with a classification probability of 0.5 were equally likely to be in either group. The misclassifications (C−, A−) are indicated and appear on the "wrong side" of the cutoff line.

3.3. Temporospatial ERP measures versus measures from a single electrode

Compared to using a single electrode [3], the addition of spatial information importantly improves the classification results (Fig. 4). We assessed this by computing the same discriminant analysis without the second spatial PCA step. Instead, only temporal ERP measures for CZ (the central midline electrode, which, due to volume conduction, is reflective of neighboring brain activity) entered the discriminant function. Using

Table 2
Linear discriminant function for discriminating between the AD and healthy control groups using temporospatial ERP scores

Temporal ERP component	Spatial factor	Experimental conditions	Discriminant coefficients	
			AD	HC
C200	Posterior	Parts: mean of 1, 2, 3, 4 Relevance: REL-IRR	−0.94	+2.45
C525	Posterior	Parts: mean of 3 and 4 Relevance: REL	−0.46	+0.74
C250	Posterior	Part: 1 Relevance: REL	−1.62	+0.40
P3	Posterior	Parts: mean of 1, 2, 3, 4 Relevance: mean of REL, IRR	−0.68	+0.55
C115	Posterior	Parts: mean of 2 and 4 Relevance: REL	+0.61	−0.50
C250	Anterior	Part: 1 Relevance: REL	−0.48	+0.35
C160	Anterior-Posterior	Parts: mean of 1, 2, 3, 4 Relevance: mean of REL, IRR	−0.43	+0.18
CNV	Posterior	Part: mean of 2 and 4 Relevance: IRR	+0.82	+0.16
C250	Posterior	Parts: mean of 1, 2, 3, 4 Relevance: IRR	+1.92	−0.15
P3	Anterior	Parts: mean of 1, 2, 3, 4 Relevance: REL	−0.79	+0.69
C200	Anterior	Parts: mean of 1, 2, 3, 4 Relevance: REL-IRR	−0.59	−2.03
Constant			−0.70	−0.91

Abbreviations: AD, Alzheimer's disease; ERP, event-related potential; HC, healthy controls.

NOTE. The stepwise discriminant procedure selected the 11 temporospatial scores listed above for the development set. These included measures from most temporal components and from both spatial factors (anterior and posterior). In addition, a variety of experimental conditions are represented. The weights (discriminant coefficients) are applied to each measure for each discriminant function (AD or healthy control). The weighted measures are summed and added to the constant to produce an AD and healthy control result for each participant. These resultant sums are then used to determine group membership (Fig. 3). Parts refer to intratrial parts and relevance refers to task relevancy within a number-letter trial.

the same combination of temporal components and experimental conditions to keep these aspects constant, we found, without the addition of empirically derived spatial information, the development analysis performed with only 74% accuracy on this same set of participants. This is in comparison with 88% accuracy using temporospatial measures (Fig. 2). The cross-validation accuracy was also markedly reduced for the single-electrode analysis to 61% from 76% in temporospatial analysis. Both of these single-electrode results are significantly less accurate than the same analysis performed with our temporospatial markers (development: $\chi^2 = 5.22$, $P < .05$, cross-validation: $\chi^2 = 3.82$, $P < .05$).

4. Discussion

Temporospatial ERP measures provide a concise, consolidated method of representing salient information about brain activity related to information processing. Our two-step PCA approach reduced a large amount of continuous data in both temporal and spatial domains to discrete measures easily attributable to experimental conditions. Discriminant analysis weighted these measures to differentiate between AD and healthy control individuals while providing a key quantitative context to that decision by posterior probabilities of group membership.

4.1. Posterior probabilities

Using the posterior probabilities provided by the discriminant function, we can separate the classifications that may be borderline or "too close to call" (Fig. 3). This can help identify individuals with confident AD classifications. Using a range of 0.40 to 0.60, eight of the 72 participants appeared in the "too close to call" area. More importantly, 64 of the 72 participants (89%) had posterior probabilities outside the "too close to call" range, and 80% of those participants were correctly classified.

These classification probabilities based on temporospatial ERP measures may add important information to a clinical diagnosis. The temporospatial ERP test misclassified 10 healthy control participants as AD, but perhaps these errors could be construed as predictions of AD (Fig. 3). The probability of AD diagnosis based on temporospatial ERP measures in an individual with clinically normal cognition might reflect early AD pathophysiology that has not reached clinical significance. This information regarding high likelihood of future phenoconversion to AD may improve early detection and guide a physician in determining pre-emptive treatment strategies. It also may aid researchers in identifying appropriate participants for preclinical trials where therapies are designed to prevent or slow phenoconversion to clinically manifest AD, potentially increasing the likelihood of these therapies' success.

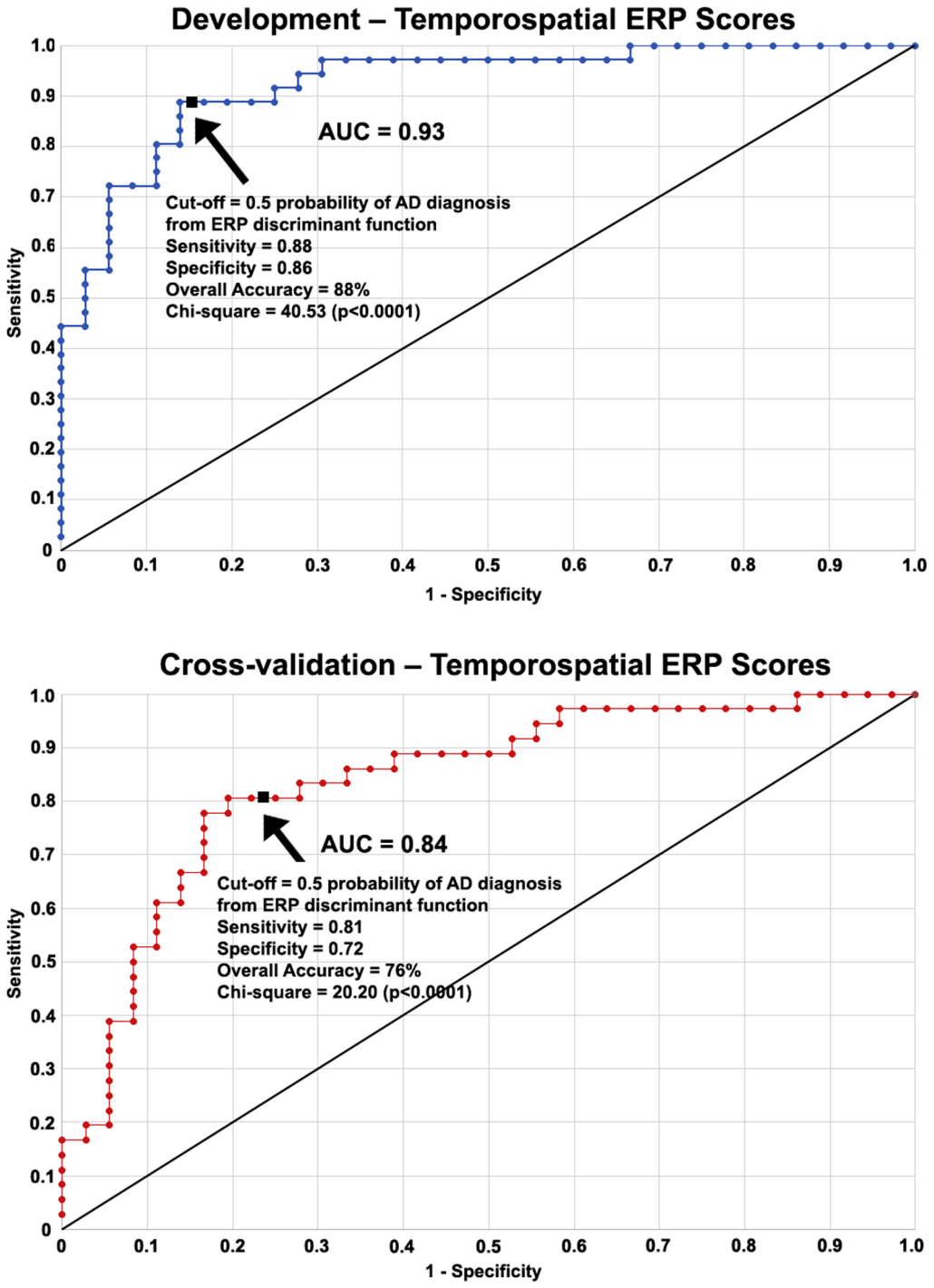

Fig. 2. ROC curves for the development and cross-validation analyses using temporospatial ERP measures to compute the discriminant functions. The development analysis involved applying the discriminant functions to the data (participants) used to develop them. The one-left-out (or jackknifed) cross-validation was performed by omitting one participant when developing the PCA structure, selecting the measures, and creating discriminant functions. The discriminant functions were then applied to the omitted participant. This was done for each participant. Area under the curve (AUC) has a maximum value of 1. Sensitivity is calculated as the number of correctly classified AD participants divided by the total number of AD participants (or true positives/[true positives + false negatives]). Specificity is calculated as the number of correctly classified healthy control participants divided by the total number of healthy control participants (or true negatives/[true negatives + false positives]). Abbreviations: AD, Alzheimer's disease; ERP, event-related potential; PCA, principal components analysis; ROC, receiver-operating characteristic.

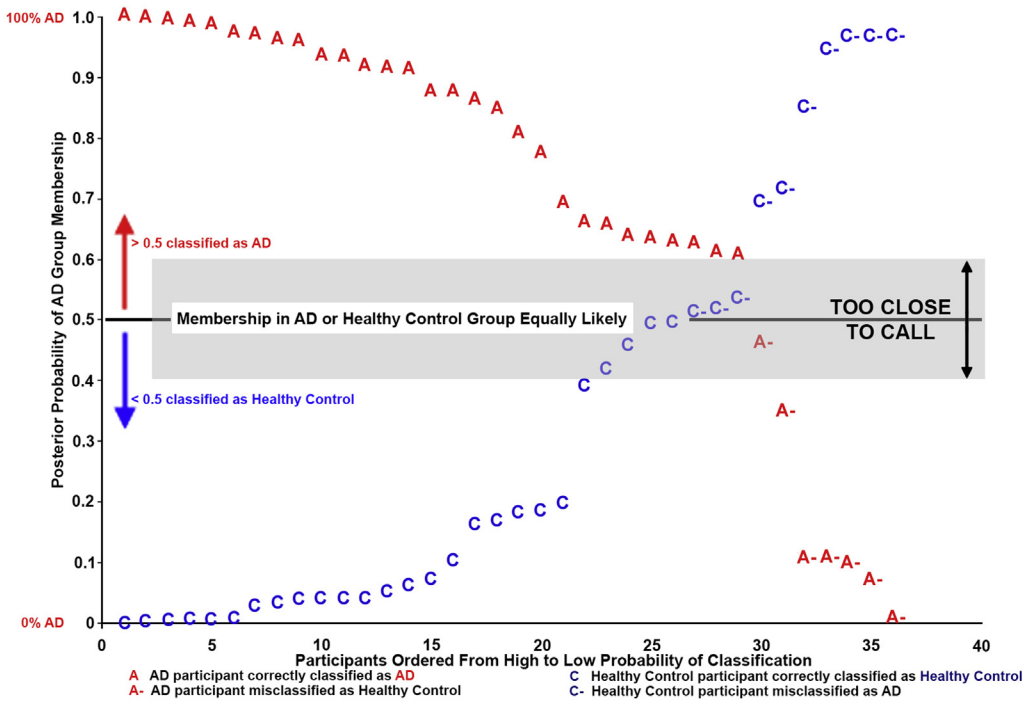

Fig. 3. Posterior probabilities for each of the 36 individual classifications belonging to the AD or healthy control group (cross-validation). A probability of 1.0 indicates complete likelihood of belonging to the AD group, 0.5 indicates the participant is equally likely of being placed in the AD or healthy control group, and 0 indicates complete likelihood of belonging to the healthy control group. Misclassified individuals are marked (−). Participants are ordered by their probability (with the most confident probabilities of an AD or healthy control diagnosis shown to the left). Those in the gray area labeled "too close to call" have probabilities too close to chance to make a confident classification. Abbreviation: AD, Alzheimer's disease.

4.2. Weighted temporospatial ERPs as markers of neurodegeneration

While many studies have investigated one or perhaps two ERP measures as discriminators of AD, we posit that the weighted contribution of many ERP measures may produce a more complete picture of degenerating brain activity and reflect the involvement of large distributed networks supporting cognitive function. In addition, with the use of temporospatial PCA, we can identify the most salient information from both the temporal waveforms and spatial distributions without threatening the degrees of freedom in the discriminant analysis. This is a key facet of our analysis, as our composite ERP measures can encompass the most important temporal, spatial, and cognitive data.

Clearly a multivariate approach to using ERPs as markers of AD is important. We have first demonstrated that a weighted combination of different ERP markers performs well as a system of identifying individuals with AD. Second, the addition of spatial information through a formal, multivariate procedure improves the classification accuracy ($P < .05$ for both development and cross-validation analyses). Spatial data could be included through averaging, but a two-step temporospatial PCA provides for data reduction while including the most salient information and, importantly, does not rely on assumptions about the spatial structure of the components.

4.3. Implications

Because ERPs are indices of brain electrophysiological activity with high temporal resolution, they may be able to add important functional information about cognitive processes that other biomarkers cannot easily provide. The results presented here are a step toward more challenging clinical questions of predicting preclinical AD and providing functional cognitive measures that can enhance other biomarkers. Further research is essential to relate these ERP biomarkers to other biomarkers, such as cerebrospinal fluid (CSF) biomarker signatures, blood biomarkers, and imaging. Recent work using CSF markers showed a comparable ROC AUC of 0.86 in classifying AD and healthy elderly using a comparable number of participants [37]. While our sample sizes are ample, a larger number of participants would permit further validation of the generalizability and reliability of the discriminant functions through applying these discriminant functions to an independent test set of participants. Also, longitudinal studies are warranted in preclinical AD individuals to assess the predictive value of our ERP measures, particularly in MCI individuals with high amyloid load or with positive blood lipid markers for dementia [38]. Because ERPs offer functional data concerning brain activity with high temporal resolution, they hold promise as a biomarker system that can enhance and possibly improve the detection of AD in older adults with reasonable probability of accurate classification.

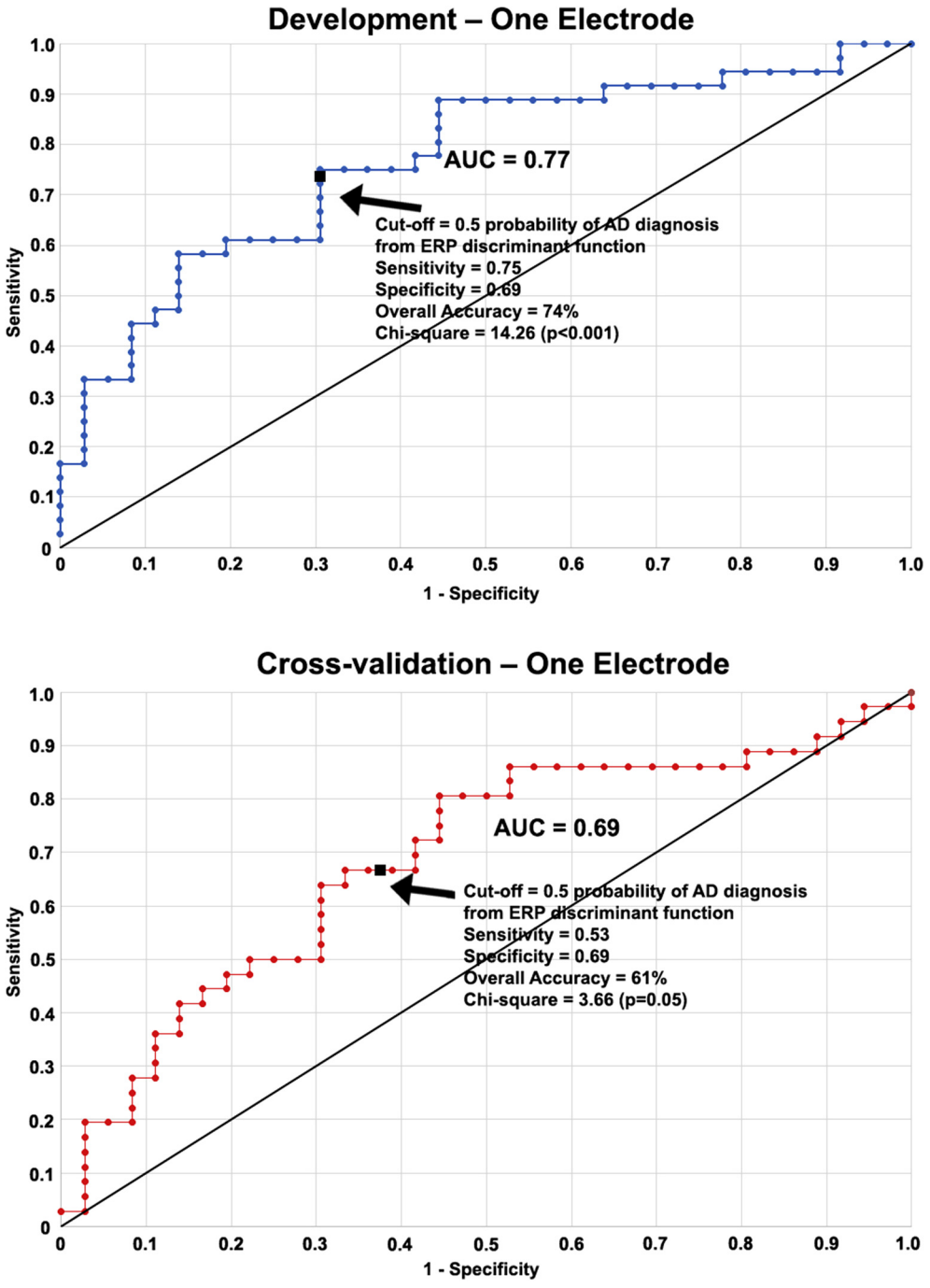

Fig. 4. ROC curves for the development and cross-validation analyses using ERP measures from a single electrode (CZ) to compute the discriminant functions. See Fig. 2 for more description of the process used to derive these results and a comparison with discriminant results using temporospatial ERP scores. Abbreviations: ERP, event-related potential; ROC, receiver-operating characteristic.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.dadm.2018.08.002.

RESEARCH IN CONTEXT

1. Systematic review: Most Alzheimer's disease (AD) biomarker research involves biochemical and/or structural measures rather than identifying functional measures related to varying cognitive processes. Brain event-related potentials (ERPs), which are inexpensive and noninvasive, show promise as functional biomarkers. However, combining spatial and temporal ERP information has not yet been attempted in AD biomarker research.
2. Interpretation: We investigated the classificatory performance of combinations of brain ERPs in individuals with AD and age-matched cognitively healthy controls. We expanded the use of ERPs to incorporate both temporal and spatial information through two-step principal components analysis. Our approach includes a quantitative measure (posterior probability) for each individual's classification. These novel ERP biomarkers performed with excellent accuracy in classifying early-stage AD and healthy controls, confirmed with significant cross-validation.
3. Future directions: Longitudinal analyses are warranted in preclinical AD individuals to investigate whether this ERP biomarker approach may aid in disease prediction.

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