Editorial Manager(tm) for Clinical Neurophysiology
Manuscript Draft

Manuscript Number:

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Article Type: Full Length Article

Section/Category:

Keywords: Alzheimer disease; diagnosis; EEG; Blind Source Separation; Amuse; filtering

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Abstract:

*** Abstract**

Objective*:* Improvement of detection of Alzheimer disease (AD) by filtering of EEG data using blind source separation (BSS) and projection of components which are possibly sensitive to cortical neuronal impairment found in early stages of AD.

Method: Artifact-free 20 s intervals of raw resting EEG recordings from 22 mild AD patients and 38 age-matched controls were decomposed into spatio-temporally decorrelated components using BSS algorithm "AMUSE". Filtered EEG was obtained by back projection of components with the highest linear predictability. Relative power of filtered data in delta, theta, alpha1, alpha2, beta1, and beta 2 bands were processed with Linear Discriminant Analysis (LDA).

Results: Preprocessing improved the percentage of correctly classified patients and controls computed with jack-knifing cross-validation from 59 to 73% and from 76 to 84%, correspondingly.

Conclusions: The proposed approach can significantly improve the sensitivity and specificity of EEG based AD diagnosis and may have potential for improvement of EEG classification in other clinical areas or fundamental research.

Significance: Since the patients with AD should be identified during large scale screening, inexpensive tools are highly needed. The developed method is quite general and flexible, allowing for various extensions.

EEG filtering based on blind source separation (BSS) improves detection of Alzheimer disease

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Introduction

Alzheimer disease (AD) is one of the most frequent disorders among the elderly population (Jeong, 2004). Recent studies have demonstrated that AD has a presymptomatic phase, likely lasting years, during which neuronal degeneration is occurring but clinical symptoms not yet appear. This makes preclinical discrimination between people who will and will not ultimately develop AD critical for early treatment of the disease which could prevent or at least slow down the onset of clinical manifestations of disease (Rapoport, 2000; Wagner, 2000; DeKosky and Marek, 2003; Blennow and Hampel, 2003). Moreover, early diagnostic tools could significantly facilitate the development of drugs for the treatment at the early stage of AD: without preclinical diagnosis, many times more subjects (potential patients with huge proportion of those who actually would never develop AD) should be involved for testing of these drugs (DeKosky and Marek, 2003). A diagnostic method should be relatively inexpensive, to make possible screening of many individuals who are at risk of developing this dangerous disease (DeKosky and Marek, 2003). The electroencephalogram (EEG) is one of the most promising candidates to become such a method. However, while quite many signal processing techniques were applied for revealing pathological changes in EEG associated with AD (see Jeong, 2004, for review), the EEG-based detection of AD is still not sufficiently reliable and further improvement of methodology is necessary.

The main idea of this paper can be formulated as "filtering based on Blind Source Separation (BSS)", that is, filtering of EEG by selection of most relevant components followed by reconstruction of the relevant part (subspace) of EEG signal using back projection of only these components. We propose a preprocessing technique based on this idea for improving EEG-based AD diagnosis (possibly useful also in other fields of EEG analysis). Its usefulness was evaluated in combination with standard procedures, namely the linear discriminant analysis (LDA) applied to spectral power in several frequency bands. To make comparison clear and fair, we used only most reliable but simple procedures. However, more sophisticated analysis based on recent advances in techniques for EEG processing, BSS and data classification may provide, in combination with proposed preprocessing, further significant improvement of early AD diagnosis, and some relevant emerging techniques will be mentioned in Discussion.

Blind Source Separation Filtering for EEG Classification

Intuitively, one can expect that some components of such a complex signal like EEG can be more sensitive to Alzheimer’s disease and the related disorders than others. These more sensitive components can be considered as useful "signal", and the other components of EEG as "noise" or “unwanted signals”. Improving the "signal-to-noise ratio" by filtering off the "noise" could enhance the performance of subsequent feature extraction and data classification. Blind Source Separation (BSS) algorithms (see Cichocki and Amari, 2003, for extensive review) can be used for the purpose of such filtering.

BSS, in its application to EEG analysis, assume that EEG signal is composed of a finite number of components (signals from the brain and other sources), $s(t) = [s_1(t), ..., s_n(t)]^T$. Here t is a discrete time index, n is the number of components and $[...]^T$ means transpose of row vector. Components are mixed through unknown linear mixing process (described by $n \times n$ mixing matrix $\mathbf{A}$), and n sensors (EEG electrodes) record the mixed signals $\mathbf{x}(t) = \mathbf{A}\mathbf{s}(t)$. Each of the components may change in time, but has a fixed weight for each channel. BSS algorithm finds an unmixing (separating) $n \times n$ matrix $\mathbf{W}$ consisted of coefficients with which the electrode signals should be taken to form, by summation, the estimated components: $\mathbf{y}(t) = \mathbf{W}\mathbf{x}(t)$. (In more general case, the number of components can be not equal to the number of sensors.) The entries of the estimated mixing matrix $\hat{\mathbf{A}} = \mathbf{W}^{-1}$ are components' weights in the mixing process; in other words, they indicate how strongly each electrode picks up each of individual components. **Back projection** of some selected components $\mathbf{x}_r(t) = \mathbf{W}^{-1}\mathbf{y}_r(t)$ (where $\mathbf{x}_r$(t) is a vector of reconstructed sensor signals and $\mathbf{y}_r$(t) is the vector obtained from the vector $\mathbf{y}(t)$ after removal of all the undesirable components (i.e., by replacing them with zeros)) allows us to filter the EEG data.

In strict sense, BSS means estimation of true (original) sources, though exactly the same procedure can be used for separation of two or more subspaces of the signal without estimation of true sources. One procedure currently becoming popular in EEG analysis is removing artifact-related BSS components and back projection of components originating from brain (e.g., Jung et al., 2000; Vorobyov and Cichocki, 2002). In this procedure, components of brain origin are not required to be separated from each other exactly, because they are mixed again by back projection after removing artifact-related components. But by the same procedure we can filter off the "noise" also in wider sense, improving the proportion of any types of useful information in the signal. Specifically, we can try to increase the proportion of signals content related to AD (i.e. to improve signal to noise ratio – SNR).

Finding the rules or fundamental principles for identification of **relevant and irrelevant components** is critical for the proposed approach and, in general, may require extensive studies. In the case of removing artifact-related components, such components typically can be easily identified by visual inspection, but in more general case exact discrimination of relevant and non-relevant components is more difficult. In this paper we attempt to differentiate clusters or subspaces of components with similar properties or features. For the purposes of EEG classification the estimation of individual components corresponding to separate and meaningful brain sources is not required, unlike in other applications of BSS to EEG processing (including its most popular variant, Independent Component Analysis (ICA)). The use of clusters of components is especially beneficial when the data from different subjects are compared: similarity between individual components in different subjects is usually low, while subspaces formed by similar components are more likely to be sufficiently overlapped. Differentiation of subspaces with high and low proportion of diagnostically useful information can be made easier if components are separated and sorted according to some criteria which, at least to some

extent, correlate with the diagnostic value of components. BSS algorithm "AMUSE", in our opinion, can be relevant for this task.

AMUSE Algorithm and its Properties

AMUSE (Tong et al., 1991, 1993; Szupiluk and Cichocki, 2001; Cichocki and Amari, 2003) is a BSS algorithm which arranges components not only in the order of decreasing variance (that is typical for the use of singular value decomposition, SVD, which is implemented within the algorithm), but also in the order of their decreased linear predictability. Low values for both characteristics can be specific for many of EEG components related to high frequency artifacts, especially electromyographic signal (which cannot be sufficiently removed by usual filtering in frequency domain, see Goncharova et al., 2003). Thus, a first attempt of selection of diagnostically important components can be made by removing a range of components separated with AMUSE (below referred to as "AMUSE components") with the lowest linear predictability. Automatic sorting of components by this algorithm makes it possible to do this simply by removing components with numbers higher than some chosen value.

AMUSE algorithm belongs to the group of second-order-statistics spatio-temporal decorrelation (SOS-STD) BSS algorithms. It provides similar decomposition as the well known and popular SOBI algorithms (Belouchrani et al., 1997; Tang et al. 2002). AMUSE algorithm uses simple principles that the estimated components should be spatio-temporally decorrelated and be less complex (i.e., have better linear predictability) than any mixture of those sources. The components are ordered according to decreasing values of singular values of a time-delayed covariance matrix. As in PCA (Principal Component Analysis) and unlike in many ICA algorithms, all components estimated by AMUSE are uniquely defined (i.e., any run of algorithms on the same data will always produce the same components) and consistently ranked. Fig. 1 illustrates typical components obtained by decomposing EEG using AMUSE algorithm.

AMUSE algorithm can be considered as two consecutive PCAs: First, PCA is applied to input data; secondly, PCA is applied to the time-delayed covariance matrix of the output of previous stage. In the first step standard or robust prewhitening (sphering) is applied as a linear transformation $\mathbf{z}(t) = \mathbf{Q}\mathbf{x}(t)$ where $\mathbf{Q} = \mathbf{R}_x^{-\frac{1}{2}}$ of the standard covariance matrix $\mathbf{R}_x = E\left\{\mathbf{x}(t)\mathbf{x}^T(t)\right\}$ and $\mathbf{x}(t)$ is a vector of observed data for time instant *t*. Next, SVD is applied to a time-delayed covariance matrix of pre-whitened data: $\mathbf{R}_z = E\left\{\mathbf{z}(t)\mathbf{z}^T(t-1)\right\} = \mathbf{U}\mathbf{S}\mathbf{V}^T$**,** where **S** is a diagonal matrix with decreasing singular values and **U, V** are matrices of eigenvectors. Then, an unmixing matrix is estimated as $\mathbf{W} = \hat{\mathbf{A}}^{-1} = \mathbf{U}^T\mathbf{Q}$ or $\hat{\mathbf{A}} = \mathbf{Q}^T\mathbf{U}$.

AMUSE algorithm is much faster than the vast majority of BSS algorithms (its processing speed is mainly defined by the PCA processing within it) and is very easy to use, because no parameters are required. It is implemented as a part of package "ICALAB

for signal processing" (Cichocki et al., online) freely available online and can be called also from current version of EEGLAB toolbox (Delorme and Makeig, 2004) (which is freely available online at http://www.sccn.ucsd.edu/eeglab/) if both toolboxes are installed.

Methods

Subjects and EEG recording

Out of our EEG database collected in the previous study (Musha et al., 2002) we selected 25 patients with mild AD and 47 age-matched controls which have relatively little artifacts. AD patients in this database had, at the time of EEG recording, only memory impairment but no apparent loss in general cognitive, behavioral, or functional status. Recording was made with eyes closed in an awake resting condition (with vigilance control) using 21 electrodes according to 10-20 system.

EEG data analysis

All computations were done using MATLAB (The MathWorks, Inc.). EEGLAB (Delorme and Makeig, 2004) was used for visual analysis of EEG recordings, and AMUSE algorithm implemented in ICALAB (Cichocki et al., online) was used for BSS processing.

EEGs were visually inspected and the first continuous artifact-free 20 s interval of each recording was chosen for the analysis. Due to the lack of such interval in some recordings, the number of patients and controls were reduced to 22 and 38, correspondingly.

Each EEG was decomposed into 21 decorrelated components by AMUSE. Some of the components (see Results) were selected for back projection, which formed preprocessed ("AMUSE filtered") EEG data. Spectral analysis based on Fast Fourier Transform (Welch method, Hanning 1s window, 2 s epochs overlapped by 0.5 s) was applied to raw data, to the components and to the projections of selected components. Relative spectral powers were computed by dividing the power in delta (1.5- 3.5 Hz), theta (3.5-7.5 Hz), alpha 1 (7.5-9.5 Hz), alpha 2 (9.5-12.5 Hz), beta 1 (12.5-17.5 Hz) and beta 2 (17.5-25 Hz) bands by the power in 1.5-25 Hz band. These values were normalized for better fitting the normal distribution using the transformation $\log(x/(1-x))$, where x is the relative spectral power (Gasser et al., 1982). To reduce the number of variables used for classification, we averaged band power values over all 21 channels.

Linear discriminant analysis (LDA) (using publicly available software for both linear classical and robust discriminant analysis, by Croux and Dehon, 2001) was used for

discriminating AD and control groups on the basis of log-transformed relative spectral power in the 6 frequency bands, averaged over channels. To improve validation of the classification results, discriminant analysis was applied in combination with jack-knifing, a procedure which typically produces lower discrimination rate than, e.g., cross-validation based on using part of a sample for learning and other part for classification, but is statistically more correct and enables increased reproducibility in other samples (Besthorn et al., 1997). Jack-knifing means that each case is classified using individual discriminant function trained with all cases except this one. Results of this procedure was used for computing sensitivity (the number of subjects who were classified as having AD and who have AD divided by the number of all subjects who have AD) and specificity (the number of subjects who were classified as normal and who are actually normal divided by number of all normal subjects).

Results

Averaged power spectra of each AMUSE component for patients and control subjects are presented in Fig. 2. As expected, components with lower numbers (corresponding to lower linear predictability) had higher relative power at lower frequencies, while components with higher numbers had higher relative power at highest frequencies. What is especially important is that the difference between patients and control subjects was clearer in the components with lower numbers (i.e., components with highest linear predictability and highest variance of their projections). Thus, in further analysis we used combination of components with lowest numbers.

To estimate how many components with highest linear predictability provides optimal classification rate, we applied LDA without jack-knifing (the latter requires much more computation time) to all projected components with numbers from 1 to 2, from 1 to 3 and so on. Overall misclassification rate was computed each time by applying obtained discriminant function to the same 60 subjects (22 patients + 38 controls). Results are presented in Fig. 3. The best classification was obtained for projection of 5 components (with numbers from 1 to 5); however, performance was high when the number of components was in a rather wide range between 3 and 9.

Classification with jack-knifing procedure was applied to projections of several combinations of components, including 1-5 which appeared to be optimal according to Fig. 2. As follows from Table 1, results of classification were better if preprocessing included selection of AMUSE components with lower numbers (1-5, 1-7, 1-10), comparing to raw data. When components with higher numbers (6-21, 8-21, 11-21) were selected in preprocessing, the results were worse than in the case of raw data. Best results were obtained with components 1-5 and 1-7 (improvement by 14% over the raw data for classification of mild AD and by 12% for control subjects), while components 11-21 gave the worst results. More detailed classification results for two combinations of components (1-5 and 1-10) and for the raw data, presented as Relative Operating Characteristic (ROC) curves in Fig. 4, confirm that use of components 1-10 only slightly improved the classification (Fig. 4a), while improvement of classification with components 1-5 over

raw data was substantial (Fig. 4b). Best classification performance after preprocessing using 1-5 components was obtained in the range of approximately 0.6-0.8 for sensitivity and 0.7-0.9 for specificity. Selection of components with high numbers was clearly not good for classification: for components 11-21 classification performance was almost at random level (Fig. 4a).

Discussion

With EEG preprocessing proposed in this paper, we obtained 80% rate of correct classification (Table 1) for mild AD using only 20 s artifact-free interval of EEG recording from each patient or control subject. While groups of patients and controls were relatively small (22 and 38, correspondingly), it should be noted that the classification performance was estimated using the rigorous jack-knifing cross-validation procedure, which reduce the risk of overstating the results. The jack-knifing procedure was applied only to LDA but not to approximate optimization of the choice of components for back projection which was made on the basis of components' spectra and preliminary run of LDA. Nevertheless, Fig. 2 and 3 suggest that the dependence of the difference between patients' and controls' spectra on component number and dependence of LDA results on the number of selected components were systematic; thus, it is unlikely that we simply picked up some random variations in LDA performance dependent on details of preprocessing and that improvement of LDA performance by preprocessing with the same parameters will be not reproducible in other groups of patients and controls.

We do not discuss here to which brain sources AMUSE components can correspond, because they can be a mixture of activity from many physical sources in the brain. This is clearly not critical for improving of EEG classification. The improvement of classification after AMUSE filtering comparing to non-preprocessed EEG data was probably caused by higher difference between patients and controls' spectra in the selected components than in the non-used (filtered off) components. Spectra computed for AMUSE components separated by BSS algorithm AMUSE (Fig. 2) demonstrate that the difference between patients and controls decreased with the number of component. Interestingly, this effect is visible at the same time in several frequency ranges: in theta range, where AD patients had typical increase of relative power, in alpha range, where typical for AD patients shift of the peak to slower frequencies was observed, and in beta range, where power was typically lower for AD patients. Components with the highest indexes showed almost no difference between patients and controls, and it was not surprising that the performance of classification based on back projection of only these components was close to random level (Fig. 4a, components 11-21). Thus, AMUSE components with higher indexes can be considered as mainly representing "noise" which makes difficult, in processing of raw EEG, to detect diagnostically important changes in characteristics of "signal". Note that "signal" and "noise" here are not labels for signal from brain sources and for artifacts: we refer to the "signal" only as to diagnostically important (significant) part (subspace) of raw EEG signal, and to "noise" as to the diagnostically not important part (non-significant subspace). AMUSE filtering, i.e., extraction of part of EEG reach with "signal" by using only "best" (here, most useful for

diagnosis) components for back projection, naturally leads to the improvement of "signal-to-noise ratio" and, as a result, to the improvement of EEG classification.

A BSS-based approach to improvement of signal-to-noise ratio in MEG signal by defining and removing noise subspace was already developed (Kawakatsu, 2003). More simple and already rather widely used technique is removing EEG and MEG artifact-related components with BSS using visual or automatic identification of such components one by one after decomposition (e.g., Jung et al., 2000). However, since in many kinds of EEG and MEG studies the goal is to extract the brain signal in possibly less corrupted form, the existing techniques are limited to removing only such part of raw signal which contain no or almost no components of brain origin but rather external artifacts and noise. In EEG classification tasks, such as diagnosis or Brain-Computer Interface (BCI), preserving the original signal is less important, noise can be defined not only as artifacts but also as any part of the signal which do not contribute to the difference between the classes of EEG which should be differentiated, and larger subspace with high proportion of such "noise" can be removed. The existing techniques can only identify, by some a priori known characteristics, noise components (Jung et al., 2000; Kawakatsu, 2003; Barbati et al. 2004) and some very specific diagnostically important components (epileptic spike separation: e.g., Kobayashi et al., 2002). Xu et al. (2004) recently suggested using a subspace approach for differentiating between task-related EEG patterns in BCI. They selected several ICA components related to P300 according to the a priori knowledge of P300 spatio-temporal pattern and reconstructed a clear P300 peak using back projection of these components. Like in the case of epileptic spikes, the components in this case were easily identifiable.

In a general case, however, important and not important components are not easily identifiable. The task becomes especially challenging if EEG components from different subjects should be compared, because the sets of components produced by BSS in different subjects usually differ dramatically. In our approach, we rank components using some empirical rule, such as their linear predictability, and select those where difference between the pathological and normal EEG is most contrasted. This made possible to achieve substantial improvement in detection of AD. To our best knowledge, no study till now investigated the application of BSS/ICA methods as preprocessing tools in AD diagnosis.

There is obviously room for improvement and extension of the proposed method both in ranking and selection of optimal (significant) components, apparatus and post-processing to perform classification task. Especially, we can apply a wide variety of BSS methods, i.e., instead of the applied and investigated second order statistics spatio-temporal decorrelation, we can exploit other new types of BSS algorithms, such as higher order statistic ICA, sparse component analysis or smooth component analysis with a suitably ordered and ranked components. Furthermore, instead of standard LDA we can use more sensitive and robust methods, such as neural networks or support vector machine (SVM) classifiers. Classification can be probably strongly improved by supplementing the set of spectral power values which we used with much different indices, such as alpha dipolarity, a new index depending on prevalence local vs. distributed sources of EEG alpha activity, which was shown to be very sensitive to mild AD (Musha et al., 2002).

Additional attractive but still open issue is that using the proposed approach, we can not only detect but also measure in consistent way the progression of AD and influence of medications. The proposed method can be also potentially useful and effective tool for differential diagnosis of AD from other types of dementia, and possibly for diagnosis of other diseases. Other areas of EEG analysis can be also possible field for the application of our preprocessing technique. For these purposes, more studies would be needed to asses of the impact of the proposed enhancement/filtering procedures on the EEG signal of interest.

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Figure 1. Example of raw EEG (a) and its components separated with AMUSE algorithm (b) for a patient with mild AD (MildAD002). AMUSE was applied to 20 s artifact-free interval of EEG, but only 2 s are shown. The scale for the components is arbitrary but linear. Note that the components are automatically ordered according to decreasing linear predictability (increasing complexity).

Figure 2. Averaged power spectra of AMUSE components 1-21. X-axis: frequency, Hz. Y-axis: transformed relative spectral power. Relative spectral power was obtained by dividing the absolute values in each frequency bin by total power in the range 1.5-25 Hz. Before averaging, the power values were normalized using transformation log(x/(1-x)) (negative values appear because of this transformation). Red: very mild AD patients (n=22). Black: control subjects (n=38).

Figure 3. LDA approximate (computed without cross-validation) misclassification rate for different number of projected components. Only components with lowest linear predictability were used, thus, data points correspond to the following combinations of components: 1,2; 1-3; 1-4; ... 1-20, 1-21.

Figure 4. Relative Operating Characteristic (ROC) curves obtained using jack-knifing for classification of very mild Alzheimer patients (N=22) versus normal controls (N=38). LDA was applied to relative power in six EEG frequency bands. Comparison between data without preprocessing and data after selection and back projection of certain AMUSE components (AMUSE filtering). (a) Selection of first 10 components, compared to the rest of components and no preprocessing. (b) Selection of first 5 components, compared to the rest of components and no preprocessing.

Table 1. Number of subjects who were correctly and incorrectly classified by discriminant analysis applied to relative power in 6 frequency bands after selection and back projection of certain AMUSE components (AMUSE filtering). Results were obtained using jack-knifing.

Figure 1a

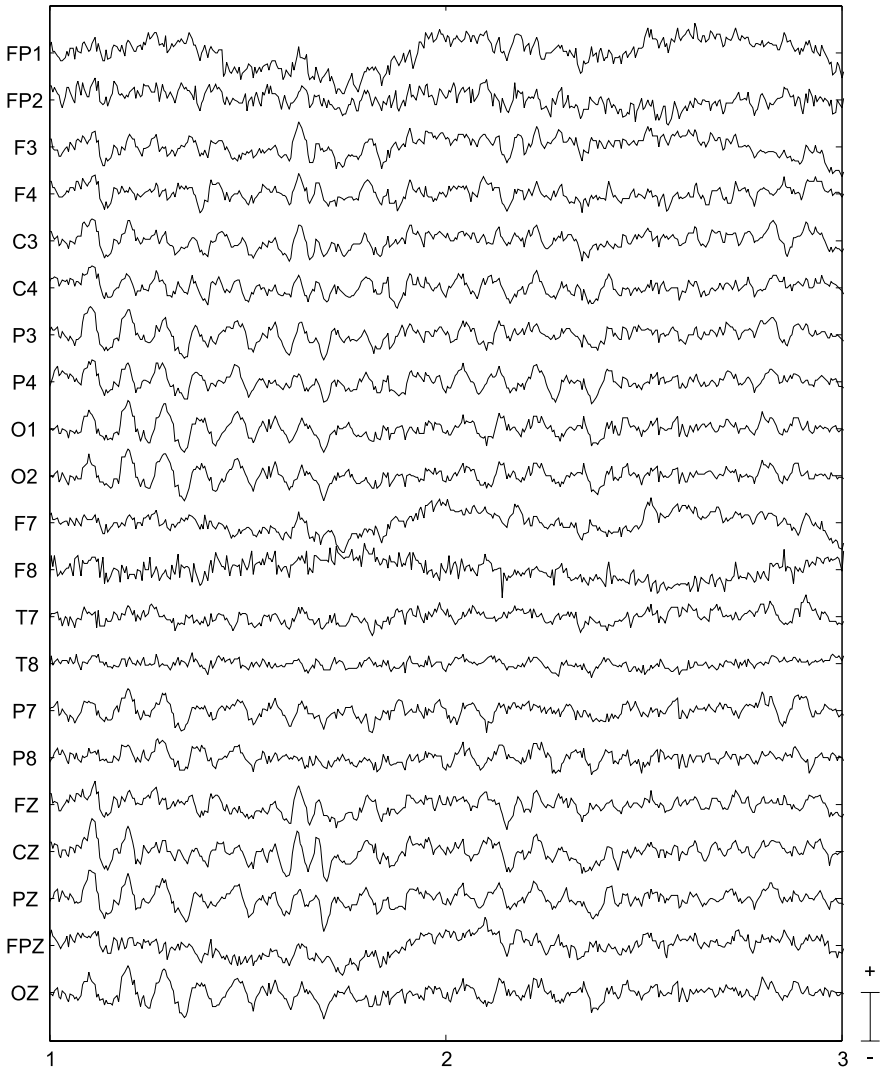

Figure 1b

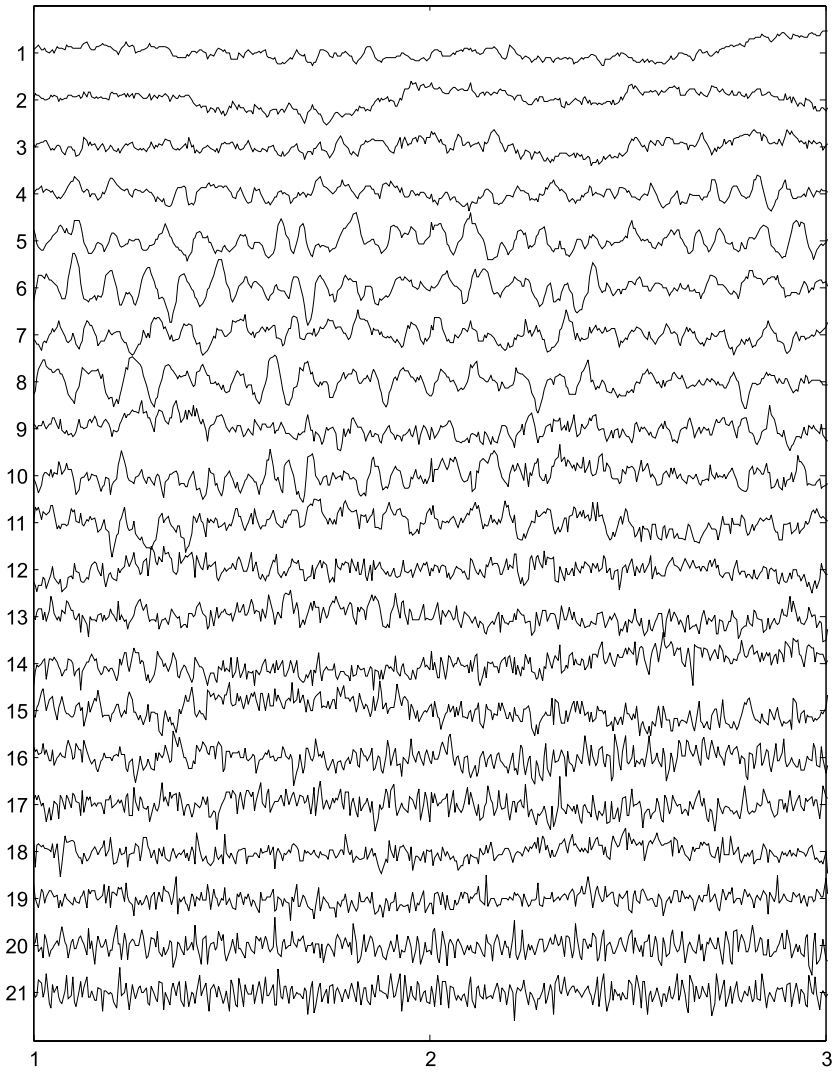

Figure 2

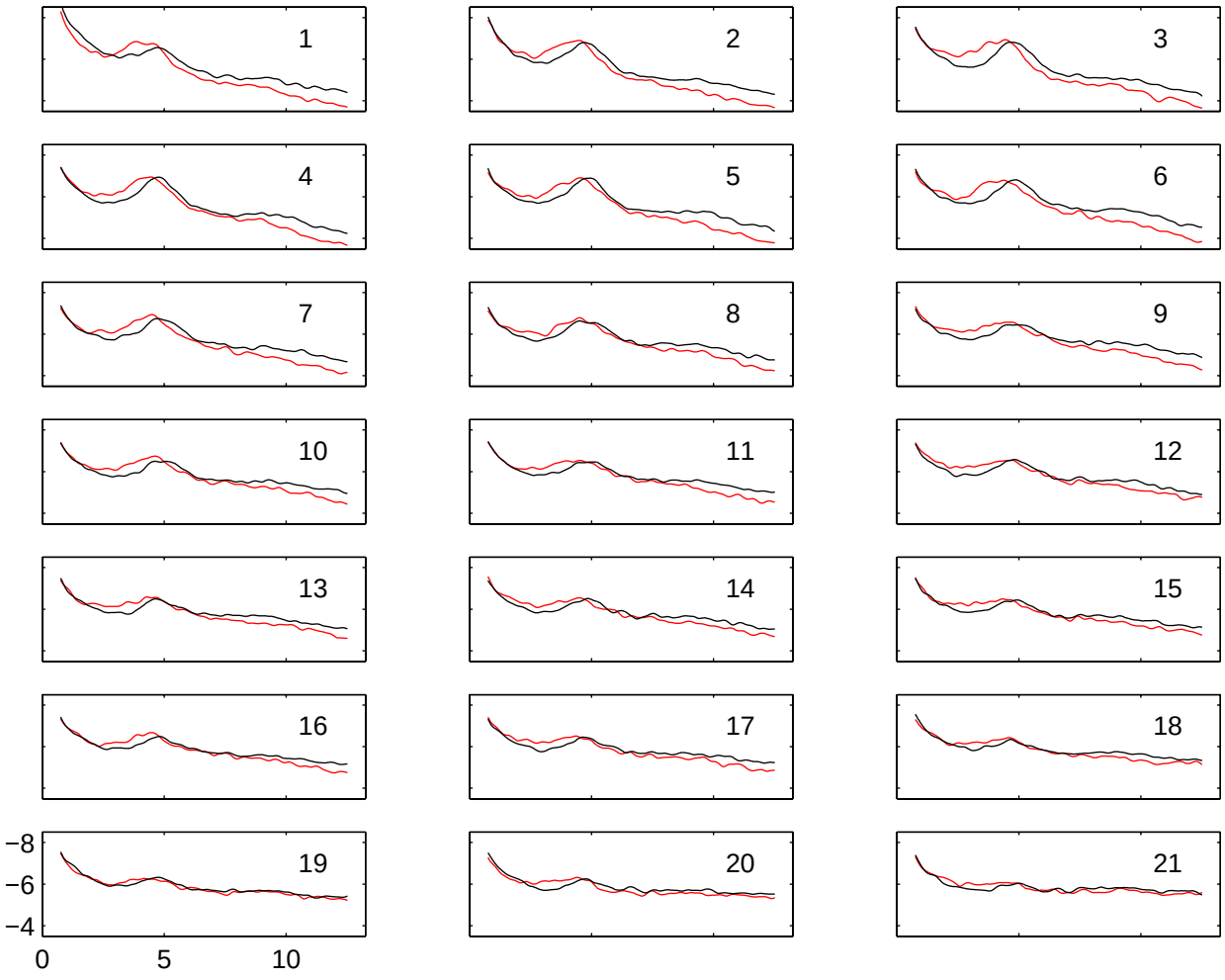

Figure 3

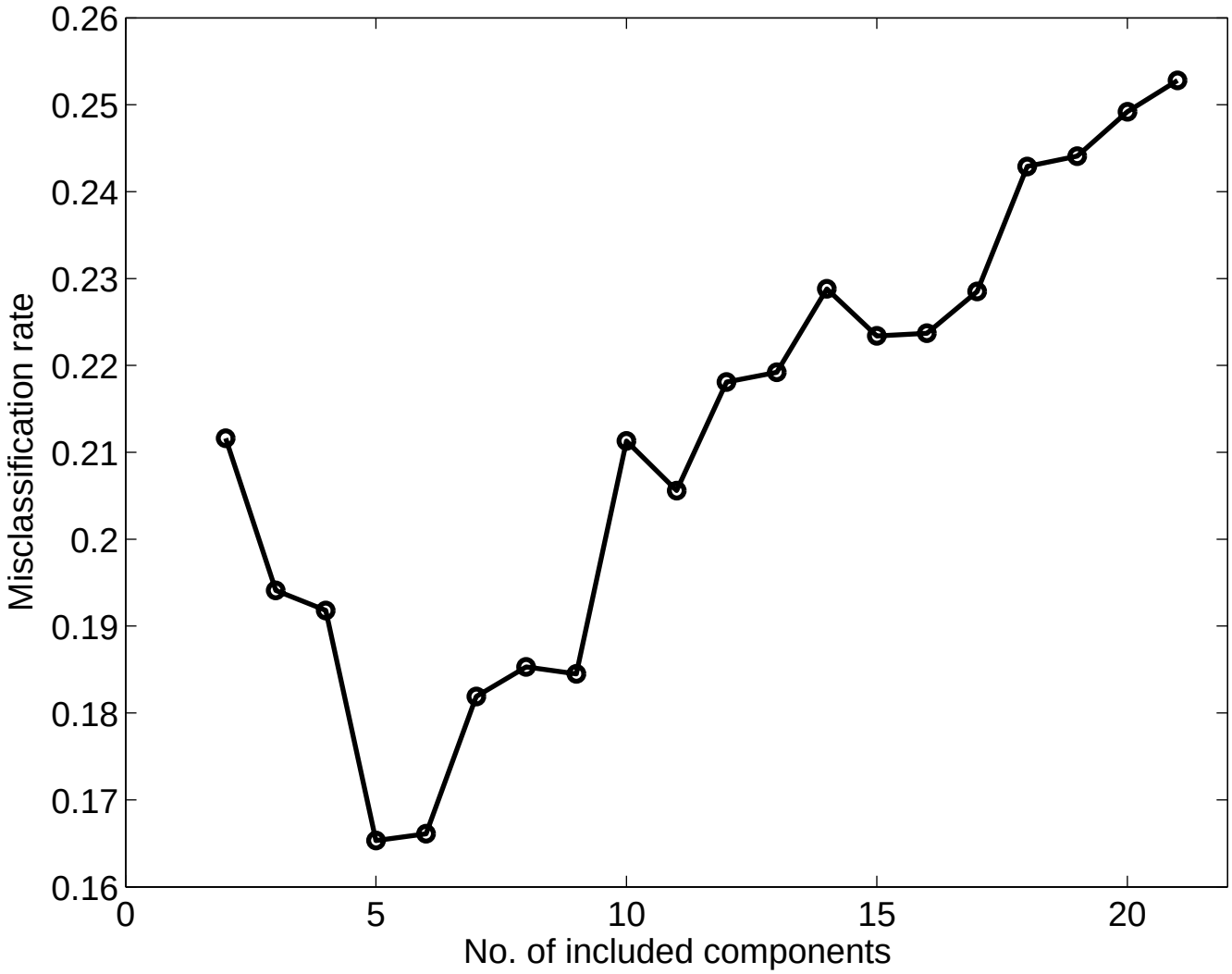
0.26
0.25
0.24
0.23
0.22
0.21
0.2
0.19
0.18
0.17
0.16
Misclassification rate
0
5
10
15
20
No. of included components

Figure 4a

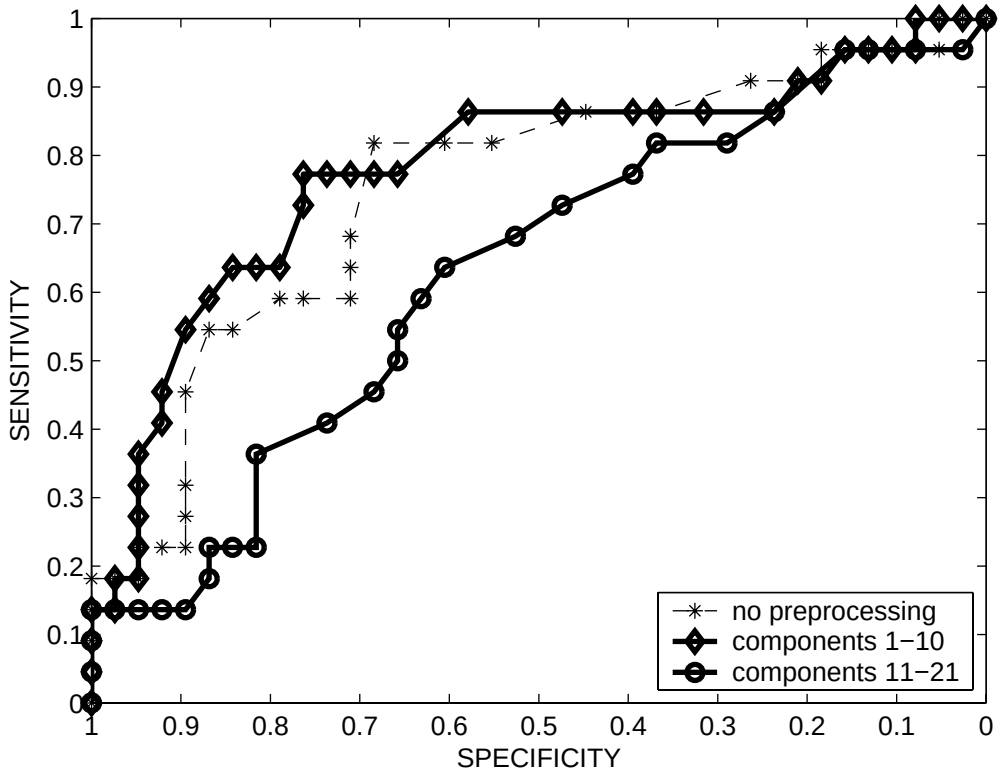
SENSITIVITY
SPECIFICITY
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
no preprocessing
components 1−10
components 11−21

Figure 4b

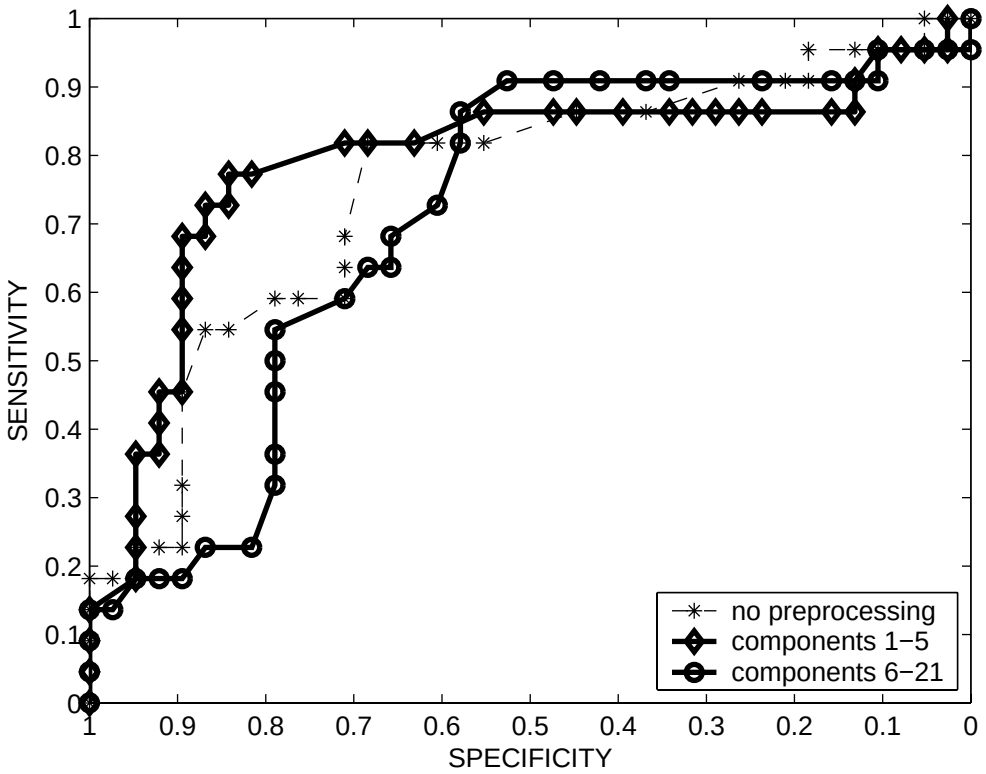
SENSITIVITY
SPECIFICITY
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
no preprocessing
components 1−5
components 6−21

Table 1

	misclassified		correc
AMUSE components selected in preprocessing	mild AD N=22	controls N=38	mild AD N=22
no preprocessing	9	9	59
components 1-5	**6**	**6**	**73**
components 1-7	**6**	**6**	**73**
components 1-10	6	9	73
components 6-21	9	11	59
components 8-21	9	11	59
components 11-21	**12**	**12**	**45**

ctly classified %	
controls N=38	all N=60
76	70
84	**80**
84	**80**
76	75
71	67
71	67
68	**60**

Author Agreement

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