

# Comparison of Blind Source Separation Preprocessings Applied to Magnetoencephalogram Recordings to Improve the Classification of Alzheimer's Disease Patients

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**Abstract.** This study compares diverse Blind Source Separation (BSS) techniques applied to magnetoencephalogram (MEG) background activity in order to improve the classification of Alzheimer's Disease (AD) patients. MEG recordings from 18 AD patients and 13 control subjects were decomposed with the following BSS algorithms: AMUSE, SOBI, FastICA, and extended Infomax. Whereas AMUSE ranked the extracted BSS components naturally, the SOBI, FastICA, and Infomax sources were ordered considering their spectral content by increasing Median Frequency (*MF*). For each BSS algorithm, a one-way analysis of variance with age as a covariate was applied to define a subset of components with the most significant differences between subject groups. Then, these relevant subsets of components were used to partially reconstruct the MEG signals. ROC curves and linear discriminant analysis were used to assess the classification of the subjects' *MF* values with and without the BSS preprocessing. The results indicated that the SOBI preprocessing increased the classification accuracy from 77.4% to 80.6% and that the algorithms AMUSE, SOBI, and extended Infomax improved the area under the ROC curve.

**Keywords:** Alzheimer's disease (AD), Blind source separation (BSS), Classification, Independent Component Analysis (ICA), Magnetoencephalogram (MEG), Median Frequency (*MF*)

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## 1. Introduction

Magnetoencephalogram (MEG) signals reflect the brain magnetic fields [Hämäläinen et al., 1993; Hari, 2005]. This recording is closely related to the commonly used electroencephalogram (EEG) [Hari, 2005]. Although both techniques measure the synchronous oscillations of the cortex directly and non-invasively, they have slightly different characteristics. For instance, the MEG is independent of any reference point and it is less affected by extra-cerebral tissues than the EEG [Hämäläinen et al., 1993; Hari, 2005]. Thus, the MEG can be useful to explore both normal and abnormal brain activities [Hari, 2005], such as the alterations caused by Alzheimer's disease (AD) [Stam, 2010].

AD causes a progressive and irreparable impairment of mental functions which leads to the patient's death [Blennow et al., 2006; Jeong, 2004]. It is the most common neurodegenerative disorder among elderly people in western countries [Blennow et al., 2006]. Moreover, AD diagnosis mostly depends on the exclusion of other dementias and can only be confirmed by necropsy [Blennow et al., 2006; Jeong, 2004]. Additionally, EEG and MEG reflect the electromagnetic activity of the cerebral cortex, which is affected by AD. Thus, these recordings have been analyzed with several signal processing techniques to gain insight into AD and, hopefully, act as a biomarker of the disease [Hornero et al., 2009; Jeong, 2004; Stam, 2010].

Although various types of analysis have measured the alterations in the AD patients' brain activity [Hornero et al., 2009; Jeong, 2004; Poza et al., 2007; Stam, 2010], it is desirable to develop new strategies to help in AD detection from the EEG and MEG analysis [Cichocki et al., 2005; Woon et al., 2007]. This can be achieved using spatial filtering methods, which help to study the EEG and MEG activity from novel perspectives [Cichocki et al., 2005; Escudero et al., 2008; 2009; Jin et al., 2002; Woon et al., 2007].

Blind source separation (BSS) denotes a set of spatial filtering techniques that estimate the constituent components or sources of a set of observations assuming a linear mixture [Cichocki, 2004; Cichocki and Amari, 2003; James and Hesse, 2005]. Some of these methodologies are also known as Independent Component Analysis (ICA). BSS has been used to remove artifacts from EEG and MEG data thanks to the fact that it can separate different types of physiological activities into different components [Escudero et al., 2007; James and Hesse, 2005].

EEG and MEG data can also be preprocessed with BSS methods to help in the detection of neurological disorders, such as AD. This is due to the fact that some BSS components of the EEG and MEG recordings may be more sensitive to this dementia than others [Cichocki et al., 2005; Escudero et al., 2008; 2009; Vialatte et al., 2005]. Hence, the most relevant sources may be selected to partially reconstruct the brain recordings [Cichocki et al., 2005; Escudero et al., 2008]. The aim is not to isolate specific brain activity, but to enhance features of AD in the partially reconstructed signals. This should lead to an improved separation between AD patients and healthy subjects [Escudero et al., 2008; 2009].

EEG and MEG were previously preprocessed with the algorithm for multiple unknown signals extraction (AMUSE) [Tong et al., 1991]. However, there is a wide variety of BSS techniques available [Cichocki and Amari, 2003; James and Hesse, 2005]. Hence, in this work, we evaluated whether other BSS methods, such as second-order blind identification (SOBI) [Tang et al., 2005], Hyvärinen-Oja's FastICA algorithm [Hyvärinen et al., 2001] and Lee-Sejnowski's extended Infomax [Lee et al., 1999], could also improve the separation of AD patients and control subjects' MEG signals.

## 2. Subjects and MEG Recording

MEG was acquired from 31 subjects. Eighteen patients (6 men and 12 women) who fulfilled the criteria of probable AD were recruited from the "Asociación de Enfermos de Alzheimer" (Spain). They were diagnosed following the guidelines of the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [McKhann et al., 1984]. Their average mini-mental state examination (MMSE) score and age were  $17.72 \pm 3.63$  and  $74.11 \pm 7.38$  years, respectively – mean  $\pm$  standard deviation (SD). No patient was receiving medication that could affect the MEG.

MEG was also recorded from 13 elderly control subjects (4 men and 9 women;  $71.38 \pm 4.84$  years, mean  $\pm$  SD) without mental diseases. The control subjects' MMSE score was  $28.92 \pm 1.04$  (mean  $\pm$  SD). The difference in age between groups was not significant ( $p$ -value = 0.2550, Student's  $t$ -test). All AD patients' caregivers and control subjects gave their informed consent to take part in this research, which was approved by the local ethics committee.

The MEGs were recorded in a magnetically shielded room with a 148-channel whole-head magnetometer (MAGNES 2500 WH, 4D Neuroimaging<sup>®</sup>) placed in the MEG Centre Dr. Pérez-Modrego at the Complutense University of Madrid (Spain). Five minutes of MEG were acquired from each of the subjects while they were lying on a patient bed with eyes closed in a relaxed state. The subjects were asked to stay awake and not to move eyes and head. The sampling frequency was 678.19Hz. Then, the recordings were down-sampled to 169.55Hz. Afterward, the data were digitally filtered between 1.5Hz and 40Hz. Finally, MEG epochs of 10 seconds (1695 sample points) that were simultaneously artifact-free at all channels were selected for further analysis.

## 3. Methodology

Our methodology is described in the following lines. Firstly, the MEG recordings were decomposed with four BSS algorithms (AMUSE [Tong et al., 1991], SOBI [Tang et al., 2005], FastICA [Hyvärinen et al., 2001], and extended Infomax [Lee et al., 1999]). Secondly, for every BSS algorithm, the extracted components were ordered to perform objective comparisons between the two subject groups [Escudero et al., 2008; 2009]. This ordering was based on previous results that showed a direct relationship between the AMUSE ranking and the spectral content of the components measured with the median frequency ( $MF$ ) [Escudero et al., 2008; 2009]. Thirdly, the  $MF$  of the AD patients and control subjects' components was compared to define, for each of the four algorithms, the range of

components with the most significant differences between AD patients and elderly controls. This selection was performed on the basis of an ANalysis Of VAriance (ANOVA) with age as a covariate. Afterward, the MEG signals were partially reconstructed using only the selected subsets of components [Cichocki et al., 2005; Escudero et al., 2008]. Finally, *MF* was applied to the partially reconstructed MEG signals and to the original recordings (without the BSS preprocessing) as a signal feature useful to distinguish the subject groups. The classification results obtained for each of the four BSS techniques were compared to the raw unprocessed recordings in order to decide which approaches improved the discrimination between AD patients and controls. The classification results were computed by means of a Linear Discriminant Analysis (LDA) and a Receiver Operating Characteristic (ROC) curve.

### 3.1. Blind Source Separation (BSS)

BSS estimates the set of  $n$  unknown underlying components,  $\mathbf{s}(t) = [s_1(t), \dots, s_n(t)]^T$ , which were linearly mixed by the full rank  $m \times n$  matrix  $\mathbf{A}$  ( $m \geq n$ ) to form  $m$  correlated recordings,  $\mathbf{x}(t) = [x_1(t), \dots, x_m(t)]^T$  [Cichocki, 2004; Cichocki and Amari, 2003; Hyvärinen et al., 2001; James and Hesse, 2005]:

$$\mathbf{x}(t) = \mathbf{A}\mathbf{s}(t). \quad (1)$$

Several assumptions are needed to estimate  $\mathbf{s}(t)$  and  $\mathbf{A}$  from  $\mathbf{x}(t)$  [James and Hesse, 2005]. The most important one is that the components must be mutually statistically independent. Alternatively, they can be considered decorrelated at any time delay. Additionally, the mixing process must be linear and instantaneous [Cichocki and Amari, 2003; Hyvärinen et al., 2001; James and Hesse, 2005]. For simplicity, we assume  $m = n = 148$  because this setting enables us to consistently compare the same number of components for each recording [Escudero et al., 2008]. With these hypotheses, BSS estimates a demixing matrix,  $\mathbf{W}$ . The estimated components,  $\mathbf{y}(t) = [y_1(t), \dots, y_n(t)]^T$ , are recovered by [James and Hesse, 2005]:

$$\mathbf{y}(t) = \mathbf{W}\mathbf{x}(t). \quad (2)$$

Some BSS components may be more affected by AD than others [Cichocki et al., 2005; Escudero et al., 2008; 2009]. Hence, the subset of the most sensitive components –  $\mathbf{y}_{subset}(t)$  – can be back projected using  $\mathbf{W}^{-1}$  to compute a partial reconstruction of the MEG signals –  $\mathbf{x}_{partial}(t)$  – that may have enhanced features of AD:

$$\mathbf{x}_{partial}(t) = \mathbf{W}^{-1}\mathbf{y}_{subset}(t). \quad (3)$$

As a result, the BSS-preprocessed signals,  $\mathbf{x}_{partial}(t)$ , may provide a better separation between AD patients and control subjects than the original MEG recordings,  $\mathbf{x}(t)$ , [Cichocki et al., 2005; Escudero et al., 2008; 2009].

### 3.2. BSS Algorithms and Ordering of the Components

Four BSS algorithms commonly used in the analysis of EEG and MEG recordings were considered in this study: AMUSE, SOBI, FastICA, and extended Infomax [Cichocki, 2004; Cichocki and Amari, 2003; Cichocki et al., 2005; Escudero et al., 2008; 2009; Hyvärinen et al., 2001; James and Hesse, 2005; Lee et al., 1999; Tang et al., 2005; Tong et al., 1991].

AMUSE and SOBI are time-structure-based methods. As these techniques assume that the components have no spatial-temporal correlations, they try to diagonalize a set of cross-covariance matrices computed from  $\mathbf{x}(t)$  [Cichocki and Amari, 2003; James and Hesse, 2005]. AMUSE decorrelates  $\mathbf{x}(t)$  at two temporal lags [Cichocki, 2004; Cichocki et al., 2005; Escudero et al., 2008; 2009; James and Hesse, 2005; Tong et al., 1991]. Moreover, it orders the components by decreasing linear predictability [Cichocki et al., 2005]. This ordering criterion is closely related to the spectral content of the extracted AMUSE components [Escudero et al., 2008; 2009]. On the other hand, SOBI uses an iterative procedure to simultaneously diagonalize multiple time delays [Cichocki and Amari, 2003; James and Hesse, 2005; Tang et al., 2005]. Considering the results of [Tang et al., 2005], SOBI was applied with 50 consecutive time lags from  $\tau = 1$  data sample to  $\tau \approx 300$  ms. As there is no fixed ordering between the SOBI sources [James and Hesse, 2005], their components were ranked by increasing *MF* on the basis of previous studies [Escudero et al., 2008; 2009].

Alternatively, FastICA and extended Infomax rely on higher-order statistics or statistical parameters like negentropy. They look for non-gaussian sources assuming that  $\mathbf{x}(t)$  are observations of

random variables where the temporal order is irrelevant [Cichocki and Amari, 2003; H yvarinen et al., 2001; James and Hesse, 2005]. In this study, FastICA was applied with the non-linearity  $\tanh(\cdot)$  and the deflationary approach [H yvarinen et al., 2001]. The extended version of Infomax was used to estimate both sub- and super-gaussian sources [Lee et al., 1999]. Similarly to the SOBI case, the FastICA and Infomax components were ranked by increasing  $MF$ .

AMUSE and SOBI decomposed signal epochs of 10 s. In contrast, FastICA and extended Infomax were applied to the whole MEG recording of five minutes per subject to have enough data samples to reliably estimate the BSS decomposition [Cichocki and Amari, 2003]. In the latter two cases, the signals were then divided into segments of 10 s and the same epochs analyzed with AMUSE and SOBI were considered.

### 3.3. Median Frequency ( $MF$ )

$MF$  was used to characterize and classify the subjects' MEG signals and to order the components estimated by SOBI, FastICA, and extended Infomax. It has been shown that  $MF$  is useful to differentiate AD patients and controls' MEG recordings [Escudero et al., 2008; Poza et al., 2007] since AD is associated with a slowing of brain activity [Jeong, 2004; Stam, 2010].  $MF$  summarizes the signal spectrum. It provides information about the relative power of the low- and high-frequency oscillations. To calculate the  $MF$ , the power spectral density ( $PSD$ ) is estimated as the Fourier Transform of the autocorrelation function [Poza et al., 2007]. Then, the  $MF$  is calculated as the frequency that contains half the  $PSD$  power:

$$\frac{1}{2} \int_{f=1.5\text{Hz}}^{40\text{Hz}} \hat{\mathbf{a}}^T \hat{\mathbf{u}} PSD(f) \hat{\mathbf{u}} = \int_{f=1.5\text{Hz}}^{MF} \hat{\mathbf{a}}^T PSD(f) \hat{\mathbf{u}}. \quad (4)$$

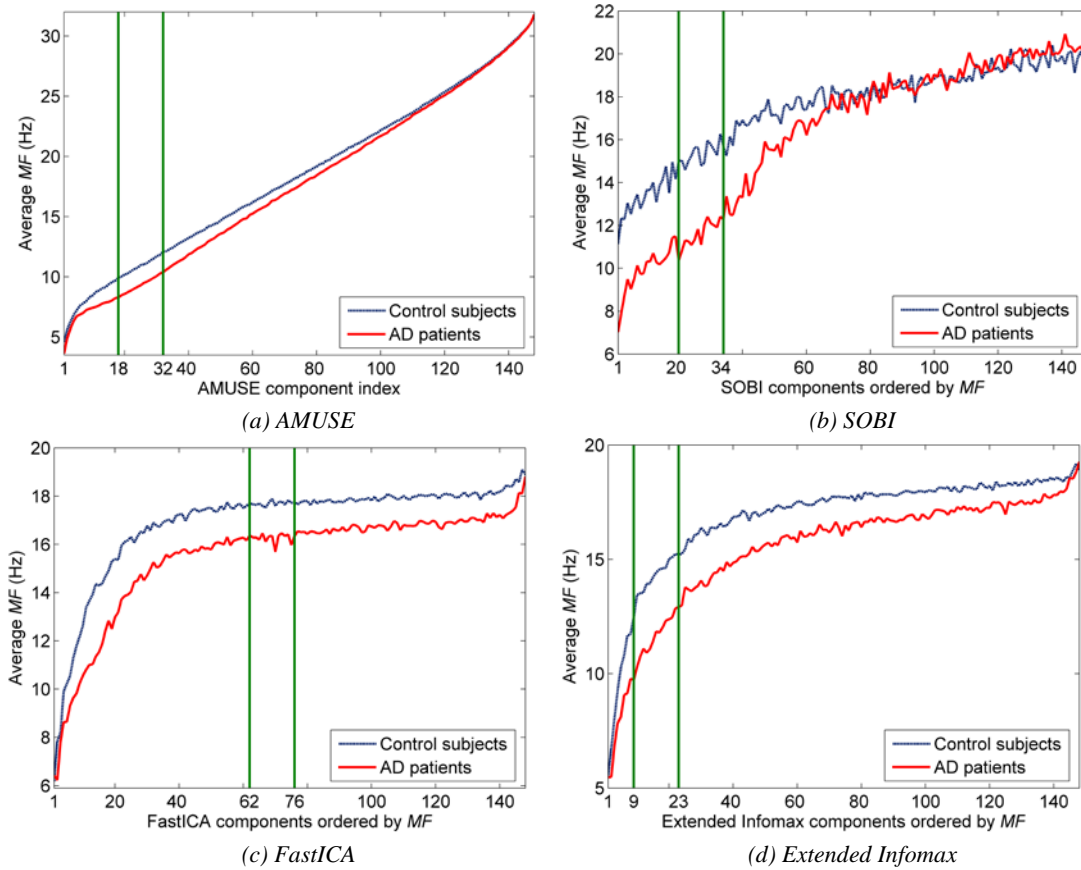
## 4. Results

Firstly, AMUSE, SOBI, FastICA, and extended Infomax were applied to blindly decompose MEG background activity recorded from 18 AD patients and 13 controls. AMUSE naturally ordered the components by decreasing linear predictability [Cichocki, 2004; Cichocki et al., 2005]. On the other hand, the components extracted with SOBI, FastICA, and extended Infomax had to be ranked in order to compare different subjects. These BSS sources were ordered by increasing  $MF$  [Escudero et al., 2008; 2009]. This ranking process was essential to the BSS preprocessing, as it allowed to directly compare the  $MF$  values of the BSS components for both subject groups [Escudero et al., 2008; 2009]. Figure 1 depicts the average  $MF$  values for each subject group, algorithm, and component index. It can be seen that AD patients are characterized by lower  $MF$  values.

Secondly, an ANOVA with age as a covariate was used to statistically assess the differences between the  $MF$  values of the subject groups for each AMUSE, SOBI, FastICA, and extended Infomax component. It was found that, for each algorithm, the components with the most significant differences tended to be gathered together. For every algorithm, we selected one subset of components to partially reconstruct the MEG signals:  $\mathbf{x}_{\text{partial}}(t)$ . These subsets were defined as the continuous intervals of 15 components (10% of all the 148 available sources) with the lowest average  $p$ -value computed as the mean of the components included into that subset. Table 1 shows these ranges, which are also represented with two vertical lines in each subplot of Figure 1.

Thirdly, four partial reconstructions of the MEG signals (one per BSS algorithm) were computed with the subsets indicated in Table 1. An average value of  $MF$  was computed per each channel and subject from these partially reconstructed signals –  $\mathbf{x}_{\text{partial}}(t)$  – and from the original MEG recordings:  $\mathbf{x}(t)$ . To simplify the classification analysis, we then computed an average value of  $MF$  per subject and type of signal:  $\mathbf{x}(t)$  without BSS and  $\mathbf{x}_{\text{partial}}(t)$  preprocessed with AMUSE, SOBI, FastICA, and extended Infomax [Escudero et al., 2008; 2009].

Finally, the corresponding Area Under the ROC Curve (AUC) and LDA were computed to assess the classification improvement due to the BSS preprocessings. The results are detailed in Table 2. Specificity was defined as the percentage of healthy subjects correctly detected whereas sensitivity represented the fraction of all AD patients for whom the test was positive. Accuracy denoted the total rate of subjects well recognized. It can be seen that the SOBI preprocessing increased the accuracy from 77.4% to 80.6% in comparison with the unprocessed recordings. On the other hand, AMUSE did not modify the classification accuracy, which decreased with FastICA and extended Infomax. Nevertheless, all BSS preprocessings apart from FastICA improved the AUC.



**Figure 1.** Average MF values of the components extracted with (a) AMUSE, (b) SOBI, and (c) FastICA, and (d) extended Infomax for AD patients and elderly control subjects. The two vertical lines indicate the subsets of 15 components with the most significant differences between subject groups.

**Table 1.** Ranges of BSS components selected to partially reconstruct the MEG signals for each algorithm: AMUSE, SOBI, FastICA, and extended Infomax.

	AMUSE	SOBI	Extend. Infomax	FastICA
Intervals of 15 components	18 to 32	20 to 34	9 to 23	62 to 76

**Table 2.** Classification results obtained from the MEG recordings without the BSS preprocessing and from the partially reconstructed MEG signals with AMUSE, SOBI, FastICA, and extended Infomax.

	AUC	Accuracy (%)	Sensitivity (%)	Specificity (%)
Without BSS	0.786	77.4	77.8	76.9
AMUSE	0.816	77.4	72.2	84.6
SOBI	0.812	80.6	83.3	76.9
FastICA	0.761	74.2	72.2	76.9
Extended Infomax	0.812	74.2	72.2	76.9

## 5. Discussion and Conclusions

AMUSE [Tong et al., 1991], SOBI [Tang et al., 2005], FastICA [Hjyvarinen et al., 2001], and extended Infomax [Lee et al., 1999] were used to decompose MEG recordings from 18 AD patients and 13 control subjects. The BSS components were characterized with the MF [Poza et al., 2007]. Moreover, this spectral feature was used to rank the SOBI, FastICA, and extended Infomax sources so that the BSS components of different subjects could be straightforwardly compared [Escudero et al., 2008; 2009]. For each algorithm, a one-way ANOVA with age as a covariate was used to determine the subset of components with the most significant average differences between AD patients and healthy elderly controls. Then, partial reconstructions of the MEG signals –  $\mathbf{x}_{\text{partial}}(t)$  – were calculated and the group separations achieved with the MF of  $\mathbf{x}(t)$  and  $\mathbf{x}_{\text{partial}}(t)$  were compared.

Only SOBI increased the classification accuracy (from 77.4% to 80.6%). However, the AUC increased (between 0.026 and 0.030) with all BSS preprocessings except for FastICA. It should be noticed that, in contrast to the maximal accuracy value, the AUC depends on the whole range of sensitivity/specificity pairs. Thus, it illustrates how separated the groups are [Fawcett, 2006]. The results suggest that AMUSE, SOBI, and extended Infomax improved the robustness of the separation [Fawcett, 2006], although the accuracy value only increased for SOBI. Yet, it is important to consider the FastICA results, as this algorithm relies on theoretical foundations that are relatively similar to those of extended Infomax [H yvarinen et al., 2001; James and Hesse, 2005]. It can be seen that the evolution of the FastICA and Infomax components with  $MF$  is similar. Moreover, the classification improvements due to time-structure-based methods (AMUSE and SOBI) are superior to those of extended Infomax and FastICA. Therefore, the former BSS methods seem to be more appropriate preprocessing tools to improve the classification of AD patients versus control subjects based on MEG recordings.

Previous research has proven the utility of BSS and common spatial patterns (CSP) techniques to improve the classification of EEGs from MCI patients who later developed AD [Cichocki et al., 2005; Vialatte et al., 2005; Woon et al., 2007]. Additionally, the current study showed that the ranges of components retained for extended Infomax and, specially, AMUSE and SOBI were similar as they have low components indexes (AMUSE) or  $MF$  values (SOBI and extended Infomax) although the first components offered less differentiation between groups. Therefore, all these studies should be considered to design a preprocessing to improve the classification of AD patients' EEG or MEG background activity. However, our work is limited by the small sample size and a validation study on a larger dataset is necessary. Additionally, the dependence of the results on the algorithms' parameters should be studied.

To sum up, we compared diverse MEG preprocessings based on the BSS techniques: AMUSE, SOBI, FastICA, and extended Infomax. The objective was to decide which techniques improved the separation between AD patients and control subjects' MEGs. Apart from FastICA, all BSS algorithms increased the AUC in comparison with the case where no BSS was used. Nevertheless, the results suggest that the time-structure-based methods could be more appropriate to improve the separation between AD patients and healthy elderly subjects.

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