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Assessment of classification improvement in patients with Alzheimer's disease based on magnetoencephalogram blind source separation

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Summary

Objectives: In this pilot study, we intended to assess whether a procedure based on blind source separation (BSS) and subsequent partial reconstruction of magnetoencephalogram (MEG) recordings might enhance the differences between MEGs from Alzheimer's disease (AD) patients and elderly control subjects.

Materials and methods: We analysed MEG background activity recordings acquired with a 148-channel whole-head magnetometer from 21 AD patients and 21 control subjects. Artefact-free epochs of 20 s were blindly decomposed using the algorithm for multiple unknown signals extraction (AMUSE), which arranges the extracted components by decreasing linear predictability. Thus, the components of diverse epochs and subjects could be easily compared. Every component was characterised with its median frequency and spectral entropy (denoted by f_{median} and $SpecEn$, respectively). The differences between subject groups in these variables were statistically evaluated to find out which components could improve the subject classification. Then, these significant components were used to partially reconstruct the MEG recordings.

Results: The statistical analysis showed that the AMUSE components which provided the largest differences between demented patients and control subjects were ordered together. Considering this analysis, we defined two subsets, denoted by BSS- $\{15,35\}$ and BSS- $\{20,30\}$, which included 21 components (15 to 35) and 11 components (20 to 30), respectively. We

partially reconstructed the MEGs with these subsets. Then, the classification performance was computed with a leave-one-out cross-validation procedure for the case where no BSS was applied and for the partial reconstructions BSS- $\{15,35\}$ and BSS- $\{20,30\}$. The BSS and component selection procedure improved the classification accuracy from 69.05% to 83.33% using f_{median} with BSS- $\{15,35\}$ and from 61.91% to 73.81% using *SpecEn* with BSS- $\{20,30\}$.

Conclusion: These preliminary results lead us to think that the proposed procedure based on BSS and selection of significant components may improve the classification of AD patients using straightforward features from MEG recordings.

Keywords: Alzheimer's disease; algorithm for multiple unknown signals extraction (AMUSE); blind source separation (BSS); magnetoencephalogram (MEG); median frequency; spectral entropy.

1. Introduction

Life expectancy has risen considerably during the last decades. In this new situation, increasing numbers of people reach ages at which mental diseases become widespread [1,2]. Among these, Alzheimer's disease (AD) is considered the most frequent cause of dementia in western countries [1,3]. Moreover, the prevalence of AD increases rapidly with age [1].

AD causes progressive and irreversible impairment of mental functions [3]. Eventually, AD patients need complete care. This dementia is characterised by neural loss. Moreover, neuritic plaques and neurofibrillary tangles also appear [1]. Whereas the former are microscopic extra-cellular depositions composed of insoluble amyloid beta-protein, the latter are intracellular twisted fibres produced by protein tau [1]. The only definitive method for AD diagnosis is direct pathological examination of brain tissue [2]. Nevertheless, a probable diagnosis based on neuroimaging techniques, medical history studies and several mental tests – e.g., Mini-Mental State Examination (MMSE) [4] – is attempted.

Due to its relevance and difficult diagnosis, the utility of the electromagnetic brain activity in the detection of AD has been widely researched in the last decades (for recent reviews, we refer to [5,6]). Both electroencephalogram (EEG) and magnetoencephalogram (MEG) record the electromagnetic oscillations produced by the pyramidal neurons non-invasively [7]. In AD, these signals show abnormalities that reflect anatomical and functional deficits of the brain cortex damaged by the dementia. Thus, the investigation of EEG and MEG signals may provide useful insights into AD [5,6].

EEG and MEG have higher temporal resolution than other brain imaging techniques, like positron emission tomography or functional magnetic resonance imaging (fMRI) [7–9]. However, there are several differences between EEG and MEG. Firstly, MEG is blind to radial currents and most sensitive to tangential dipoles. On the contrary, EEG records all primary currents [8,9]. Secondly, since EEG recordings measure the difference between the electric potential at two locations, they require to define an electrical reference electrode [7]. The selection of this electrode is a crucial matter [10]. In contrast, MEG does not need to define a reference sensor to record the brain magnetic field [8]. Finally, MEG is not affected by the conductivity of the skull and scalp, while EEG is distorted by these tissues [8,9]. Due to these characteristics, MEG is considered a complementary signal to EEG [8] that may provide a useful insight into the electromagnetic brain activity [6].

Visual inspection of the electromagnetic brain recordings from AD patients at rest with eyes closed shows a reduction in beta and alpha activity and a slowing of the cortical posterior rhythm, among other abnormalities [5]. Moreover, diverse research works confirmed this slowing applying computerised spectral analysis to EEG and MEG data. For instance, several studies quantified the changes that AD produces in the power of different frequency bands [5,11–13]. These findings agree with the fact that AD patients' EEG and MEG recordings have a lower mean frequency than those of healthy control subjects [11,13–16]. AD also causes other abnormalities in the electromagnetic brain activity, such as a decrease in the functional connectivity among cortical areas. This reduction can be measured performing a coherence analysis of brain recordings [5,10,12].

In addition to the aforementioned changes, the irregularity of the AD patients' EEG and MEG spectra also decreases [16,17]. This reduction can be evaluated using spectral entropy [18,19], which is computed applying the Shannon entropy to the normalised power spectral density (*PSD*) function. Moreover, the AD patients' EEG and MEG data have also been studied with various non-linear techniques [5,6,17,20] like complexity estimators [21–23] or connectivity measures [24,25]. Other works have focused on the internal equivalent generator dipoles of MEG activity in AD [26].

Nevertheless, there is room for further improvement in those methodologies [27]. A technique that may improve the subject classification based on features extracted from EEG and MEG data is blind source separation (BSS) [28,29], since this methodology allows us to examine these signals from another point of view [27,30].

Typically, BSS techniques are applied to a set of temporally and spatially correlated measurements, like EEGs and MEGs, although they can also be used with single channel recordings [31]. From the correlated recordings, the BSS methods estimate a number of underlying components, or sources, blindly (i.e., the components themselves and the mixing process that produced the observed measurements from the components are unknown) [28,29,32]. To estimate the underlying components, it is assumed that they are mutually independent or, alternatively, that their waveforms have no spatial and temporal correlations [29].

It should be noted that the BSS components are neither equivalent current dipoles nor fMRI activated zones. Instead, they are concurrent,

spatially and temporally decorrelated electromagnetic activities which were added over the scalp to originate the measured recordings [28,33].

Given the fact that BSS is able to isolate dissimilar kinds of activity into different components [29,32], this technique has been used to reject artefacts from EEG [33–36] and MEG [37,38] data. Once the BSS has isolated the artefacts into a few components, the brain recording is reconstructed using only the non-artefactual components [29,36]. In this way, artefacts can be removed from EEG or MEG data with minimal interference in brain activity. Likewise, BSS can be used to separate specific brain activity, such as epileptiform discharges, in order to assist in further analyses [39]. Moreover, BSS methods can be applied to brain recordings using another approach. Considering the intrinsic complexity of the brain recordings, some BSS components may have certain features that could make them more sensitive to particular brain states, such as AD [27] or audiovisual stimulation [30]. Hence, the most relevant components may be selected and the brain recordings may be partially reconstructed using only these components [27]. Thus, diverse brain states might be better differentiated in comparison to the situation where BSS is not used. Nevertheless, despite the advantages that this approach may provide, few studies have implemented it. To our knowledge, this methodology has only been applied to EEG data in [27,40].

In this study, we applied a BSS algorithm to background MEG recordings from AD patients and control subjects. Two spectral variables (median frequency and spectral entropy, denoted by f_{median} and $SpecEn$, respectively) were used to characterise every MEG channel and BSS component. The BSS components of both groups were analysed to assess how f_{median} and $SpecEn$

varied within them and to decide which provided the most relevant information to classify the subjects. In addition, the classification accuracies achieved with and without the BSS preprocessing were compared. We wanted to test the hypothesis that this procedure of BSS and subsequent selection of AD-relevant components might improve the classification of AD patients versus control subjects based on MEG background activity.

2. Subjects and signals

2.1. Subjects

Twenty-one AD patients participated in this study. The average age of this subject group, which was formed by 13 women and 8 men, was 73.19 ± 9.22 years – mean \pm standard deviation (SD) –. All AD patients were recruited from the “Asociación de Familiares de Enfermos de Alzheimer” (Spain) and fulfilled the criteria of probable AD according to the guidelines provided by the National institute of neurological and communicative disorders and stroke – Alzheimer's disease and related disorders association (NINCDS-ADRDA) [41]. The diagnosis was based on brain scans and thorough medical, physical, neurological, psychiatric and neurophysiological examinations. MMSE was used to assess the severity of AD [4]. The patients' average MMSE score was 17.95 ± 3.97 (mean \pm SD). The MEG recording was carried out when AD was diagnosed. No patient received medication that could affect the MEG signals.

In addition, 21 control subjects (age = 70.19 ± 6.96 years, mean \pm SD; 13 women) without past or present neurological or psychiatric diseases were recruited to participate in this study. The difference in age between both subject groups was not significant (p -value = 0.1861, Mann-Whitney

U-test). The average MMSE score for the controls was 29.05 ± 0.97 (mean \pm SD).

All AD patients' caregivers and all control subjects gave their informed consent to participate in this study, which was approved by the local ethics committee.

2.2. Magnetoencephalogram recording

MEGs were recorded in a magnetically shielded room using a 148-channel whole-head magnetometer (MAGNES 2500 WH, 4D Neuroimaging). During the recording process, the subjects lay on a patient bed with eyes closed. In order to avoid artefactual contamination, they were asked to stay awake and not to move eyes and head. Five minutes of MEG recording were acquired from each subject at a sampling frequency of 678.17 Hz using a hardware band-pass filter with cut-off frequencies at 0.1 Hz and 200 Hz. To reduce data length, these recordings were decimated to 169.55 Hz. This procedure consisted of filtering the recordings according to the Nyquist criterion and down-sampling them by a factor of four. Then, the recordings were copied as ASCII files to a personal computer. They were processed with a 50 Hz notch filter and a band-pass finite impulse response filter designed with a Hamming window with cut-off frequencies at 1.5 Hz and 40 Hz. MEG epochs of 20 s (3390 samples) that were simultaneously artefact-free at all channels were selected for analysis.

3. Methods

3.1. Blind source separation

Briefly, BSS techniques attempt to find the set of n unknown underlying components, $\mathbf{s}(t) = [s_1(t), s_2(t), \dots, s_n(t)]^T$, where T denotes the transpose of a vector or matrix and t is the discrete time index, which form the m temporally and spatially correlated measured signals, $\mathbf{x}(t) = [x_1(t), x_2(t), \dots, x_m(t)]^T$ [28,29,32]. Hence, in this study, $\mathbf{s}(t)$ represents the BSS components, whereas the MEG recordings are denoted by $\mathbf{x}(t)$. The mixing process is assumed to be linear [28,34,35]. Mathematically:

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

where \mathbf{A} is a full rank $m \times n$ mixing matrix and $\mathbf{x}(t)$ and $\mathbf{s}(t)$ are centred [28,29].

External noise may be included in the model [36,38]. However, for the sake of simplicity, the noise term has not been incorporated in this study [34,35]. In addition, the number of BSS components must be less than or equal to the number of recorded signals ($m \geq n$) [29]. Taking into account that only the most relevant components will be retained for further MEG reconstruction and classification analysis, we set $m=n$ instead of applying a dimensionality reduction technique in advance.

In order to estimate $\mathbf{s}(t)$ and \mathbf{A} , several hypotheses are made [28,29]. The most important assumption may be that the BSS components are mutually independent or, on the other hand, that they should be decorrelated at any time delay. In addition, it is hypothesised that the mixing process is linear and instantaneous. All these requirements are suitably met by EEG and MEG data [29].

Under these hypotheses, some BSS algorithms use the temporal dependences of the recordings to find a demixing matrix, \mathbf{W} , [28,29].

Using \mathbf{W} , the recovered BSS components vector, $\mathbf{y}(t) = [y_1(t), y_2(t), \dots, y_m(t)]^T$, which estimates $\mathbf{s}(t)$, is computed by:

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

Some BSS components of the MEG recordings may be more affected by AD than others [27]. Thus, a vector formed by the subset of the most sensitive components - $\mathbf{y}_{subset}(t)$ - could be used to compute a partial reconstruction of the MEG recordings - $\mathbf{x}_{partial}(t)$:

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

Hence, it could be assumed that some remarkable features of AD may be enhanced in $\mathbf{x}_{partial}(t)$ by comparison with the raw recordings, $\mathbf{x}(t)$ [27].

However, it should be noted that a certain order or clustering is needed to compare BSS components extracted from different MEG epochs and subjects [27,30]. Thus, among the BSS algorithms available, we used the algorithm for multiple unknown signals extraction (AMUSE) [28,42] to decompose the MEGs. This algorithm orders the extracted components by decreasing linear predictability [27].

3.2. Algorithm for multiple unknown signals extraction

Several BSS algorithms are based on the hypothesis that BSS components should have no temporal and spatial correlations [28]. Consequently, this kind of algorithms find \mathbf{W} by minimising the cross-correlations between components at certain time delays [29]. One of these algorithms is AMUSE, which decorrelates the signals at two time lags (typically, $\tau = 0$ and $\tau = 1$) [27,29,36,42]. Since only two time delays are considered in AMUSE, its computational complexity is low [27,28].

Furthermore, AMUSE always offers the same separation when it is applied to the same input data set and it orders the components by decreasing linear predictability [27]. This inherent order enables us to compare AMUSE components from different epochs and subjects straightforwardly. Thus, the definition of the subsets $\mathbf{y}_{subset}(t)$ can be done by removing the AMUSE components whose index is higher and/or lower than certain thresholds.

First of all, AMUSE applies a principal component analysis to the input data, $\mathbf{x}(t)$, in order to whiten them [27,42]. Let $E\{\cdot\}$ be the expectation value of a variable. Then, the covariance matrix of $\mathbf{x}(t)$ is:

$$\mathbf{R}_x(0) = E\{\mathbf{x}(t)\mathbf{x}(t)^T\}. \quad (4)$$

The whitened data, $\mathbf{z}(t)$, are computed by [27]:

$$\mathbf{z}(t) = \mathbf{Q}\mathbf{x}(t), \quad (5)$$

where $\mathbf{Q} = [\mathbf{R}_x(0)]^{-1/2}$.

Afterwards, the signals are decorrelated at a particular time delay, τ (usually $\tau = 1$) [27,28,36]. A time-delayed covariance matrix is computed [42] as:

$$\mathbf{R}_z(\tau) = E\{\mathbf{z}(t)\mathbf{z}(t-\tau)^T\} \quad (6)$$

and the eigenvalue decomposition of $(\mathbf{R}_z(\tau) + \mathbf{R}_z(\tau)^T)/2$ is calculated. If \mathbf{V} denotes the eigenmatrix computed from this decomposition, the demixing matrix \mathbf{W} is estimated as [42]:

$$\mathbf{W} = \mathbf{V}^T \mathbf{Q}. \quad (7)$$

As it has been described, AMUSE consists of a whitening process followed by a singular value decomposition. Thus, the computational complexity of this algorithm is low [27]. In a Matlab[®] 7.0 environment

running on a personal computer with a Intel Pentium Duo® 2.80 GHz processor and 2 GB RAM, the decomposition of the 148 MEG channels into the 148 AMUSE components took 0.4023 ± 0.0088 seconds per epoch (mean \pm SD).

3.3. Feature extraction

Two spectral features were used to characterise the MEG signals and the AMUSE components: f_{median} and $SpecEn$. Firstly, we computed the PSD of each MEG channel or AMUSE component for every epoch. $PSDs$ were calculated as the Fourier transforms of the corresponding autocorrelation functions. Then, the $PSDs$ estimated from the epochs available were averaged for each subject and MEG channel or AMUSE component. Finally, f_{median} and $SpecEn$ values were computed from the mean $PSDs$.

f_{median} is accepted as a simple way to summarise the spectral content of the PSD [16]. It has been used to study the spectra of AD, mild cognitive impairment (MCI) or vascular dementia patients' brain recordings [11,13–16], among other mental diseases. f_{median} is defined as the frequency which contains half the PSD power. Taking into consideration the cut-off frequencies of the band-pass filter applied to the MEG signals (1.5 Hz and 40 Hz), f_{median} was computed as:

$$\frac{1}{2} \left[\sum_{f=1.5\text{Hz}}^{40\text{Hz}} PSD(f) \right] = \sum_{f=1.5\text{Hz}}^{f_{median}} PSD(f). \quad (8)$$

Additionally, we estimated the $SpecEn$ in order to quantify the flatness of the PSD . $SpecEn$ is computed applying the Shannon's entropy to the normalised PSD (PSD_n) [18,19]:

$$SpecEn = -\frac{1}{\log(N)} \sum_{f=1.5Hz}^{40Hz} PSD_n(f) \log[PSD_n(f)], \quad (9)$$

where N is the number of frequency bins and the division by $\log(N)$ normalises the $SpecEn$ to a scale from 0 to 1.

High $SpecEn$ values are due to broad and flat spectra (e.g., white noise), whereas this entropy estimator provides low values for spectra whose energy is mainly focused round a narrow frequency band (e.g., a sine wave). Thus, $SpecEn$ measures the disorder of the spectrum, estimating the signal irregularity [18]. Several studies have applied $SpecEn$ to electromagnetic brain signals [18,19], including the analysis of AD patients' EEGs [17] and MEGs [16].

3.4. Statistical analysis

Mann-Whitney U-test was used to decide whether there were statistically significant differences between both subject groups in the f_{median} and $SpecEn$ values of the AMUSE components. The Bonferroni correction was applied to the Mann-Whitney U-test p -values in order to avoid spurious positives. Previously, homoscedasticity was verified with the Brown-Forsythe test, and Kolmogorov-Smirnov test assessed whether the differences in the shape of the distributions were negligible.

A leave-one-out cross-validation procedure, together with receiver operating characteristics (ROC) curves [43], was used to measure the ability of f_{median} and $SpecEn$ to distinguish AD patients from control subjects when different AMUSE component subsets were retained. ROC plots analyse the performance of a certain variable in classifying two groups. In this study, sensitivity is defined as the rate of AD patients properly classified,

whereas specificity represents the percentage of control subjects correctly detected. Accuracy denotes the total fraction of subjects precisely identified. ROC curves also offer visual information about the quality of the classification rule, as they plot the sensitivity/{1-specificity} pair of values for all possible cut-off points. Furthermore, leave-one-out cross-validation avoids the appearance of over-fitting and bias in the analysis. The leave-one-out cross-validation classifies each single case using the decision rule obtained from the ROC analysis of all remaining data. Then, this process is repeated for all cases. Although this procedure typically reduces the sensitivity, specificity and accuracy values, it increases the reproducibility of the results [27].

In addition, correlations between AD patients and control subjects' MMSE scores and their average values of f_{median} and $SpecEn$ were assessed with Spearman's rank correlation coefficient (ρ) when different AMUSE component subsets were retained. The corresponding p -values for testing the hypothesis of no correlation against the alternative that there is a non-zero correlation were also estimated. Correlation was considered significant when the p -value was below 0.01.

4. Results

First of all, we used AMUSE to decompose MEG background activity epochs of 20 s (3390 samples) from 21 AD patients and 21 control subjects. Thanks to the inherent order of the AMUSE components, it was straightforward to compare them between groups. Thus, mean $PSDs$ were calculated for each subject and each AMUSE component index. These average $PSDs$ were characterised with f_{median} and $SpecEn$. Fig. 1 shows the

average f_{median} values for each AMUSE component and subject group. The f_{median} increased with the AMUSE component index. This suggests that the decreasing linear predictability order provided by AMUSE is indeed determined arranging the components by their spectral content, from low to high frequency oscillations. Moreover, the typical slowing of AD patients' brain recordings can also be observed in Fig. 1, since the average f_{median} values were lower for the demented patients' components than for those of the control subjects. In addition, Fig. 2 depicts the mean $SpecEn$ values of both groups for each AMUSE component. $SpecEn$ evolved similarly for both kinds of subjects. Moreover, since this entropy estimator measures the spectral irregularity and AMUSE orders the components by decreasing linear predictability, the $SpecEn$ of the components rose with the AMUSE index, until it reached values close to 1. In addition, $SpecEn$ values were usually higher in control subjects than in AD patients. This illustrates that AD patients have a MEG background activity with a narrower spectral content than control subjects.

Visual inspection of both Fig. 1 and 2 suggested that the most AD-sensitive components had indexes which varied from 5 to 60, approximately. In order to evaluate the statistical significance of the differences between groups, we carried out a Mann-Whitney U-test with a Bonferroni correction. Fig. 3 summarises the results of this analysis. Differences were usually more significant using f_{median} than $SpecEn$. Moreover, it can be seen that the largest differences were focused around indexes ranging from 10 to 40 with $SpecEn$ and from 15 to 55 using f_{median} . Taking this into consideration, we chose two small subsets of AMUSE components to partially reconstruct the MEG recordings. The first one

contained 21 components (15 to 35), and it was denoted by BSS- $\{15,35\}$. The second subset was formed by 11 AMUSE components: from 20 to 30 (BSS- $\{20,30\}$). The classification results achieved with the selection of these two subsets were compared to those provided by the MEG recordings without BSS.

For each of the three cases (without BSS, BSS- $\{15,35\}$ and BSS- $\{20,30\}$), an average *PSD* per channel and subject was computed. Two variables, f_{median} and *SpecEn*, were calculated from the *PSD* functions. After computing them, we obtained 148 values for each of the 21 AD patients and 21 healthy controls. Owing to the high spatial density of the MEG channels, it may be helpful to reduce the problem dimensionality in order to simplify the analysis and the interpretation of the results. Thus, we averaged the 148 f_{median} or *SpecEn* variables for each subject. Hence, the classification analysis was carried out using one mean value of f_{median} or *SpecEn* per subject.

A ROC analysis combined with a leave-one-out cross-validation procedure was used to evaluate the classification achieved by f_{median} and *SpecEn* in each of the three cases (without BSS, BSS- $\{15,35\}$ and BSS- $\{20,30\}$). Table 1 shows the sensitivity, specificity and accuracy values obtained with f_{median} . The average values for each subject group are also displayed. AD patients had lower f_{median} values than control subjects. It can be noticed that the SD was larger for the case where no BSS was used than for BSS- $\{15,35\}$ or BSS- $\{20,30\}$. This suggests that the component selection procedure reduced the inter-subject group variability of f_{median} . Furthermore, both cases, BSS- $\{15,35\}$ and BSS- $\{20,30\}$, improved the accuracy of the subject classification more than 11%. The accuracy without

BSS was 69.05%. In contrast, it reached 80.95% for BSS- $\{20,30\}$ and 83.33% when the subset BSS- $\{15,35\}$ was used. In addition, Fig. 4 illustrates the average ROC curves associated with these analyses. The ROC plots related to BSS- $\{15,35\}$ and BSS- $\{20,30\}$ are akin. The areas under their ROC curves are larger than that obtained without BSS, indicating a better diagnostic test when the component selection preprocessing is used.

The ability of *SpecEn* to distinguish AD patients from control subjects was also evaluated in the three studied cases. The classification results (sensitivity, specificity, accuracy and mean \pm SD for both groups) are summarised in Table 2. AD patients' MEG background activity is more regular than control subjects' one, as the *SpecEn* values were lower for the former. Likewise f_{median} , the SD of the *SpecEn* values decreased when the MEG was partially reconstructed. For this variable, the BSS and component selection procedure provided an accuracy improvement about 10% (71.43% and 73.81% for BSS- $\{15,35\}$ and BSS- $\{20,30\}$, in that order, against 61.91% for raw MEG recordings). Furthermore, the corresponding ROC plots are depicted in Fig. 5. They confirm the higher quality of the diagnostic test applied to BSS-processed signals than that based on MEG recordings without the BSS preprocessing.

Finally, we assessed whether the severity of the dementia, measured with the MMSE, was correlated with the average values of f_{median} and *SpecEn* for each case. All the computed p values, which are shown in Table 3, were significant (p -value < 0.01). There were slight increases in the correlation coefficients when the BSS and partial reconstruction was applied (BSS- $\{15,35\}$ and BSS- $\{20,30\}$) in comparison with the case where no BSS was used.

5. Discussion and conclusions

In this study, we used the AMUSE algorithm [28,42] to decompose artefact-free MEG epochs of 21 AD patients and 21 control subjects. Every AMUSE component was characterised with f_{median} [16] and $SpecEn$ [18,19], and the evolution of these spectral features with the AMUSE component index was analysed. Mann-Whitney U-test determined which components offered the most significant differences between both subject groups. Afterwards, two component subsets were selected to partially reconstruct the MEG recordings. These subsets were formed by the components BSS- $\{15,35\}$ and BSS- $\{20,30\}$. Finally, the accuracy achieved in each of these two cases, when either f_{median} or $SpecEn$ was used to classify the subjects, was compared to that obtained from the MEG recordings without BSS.

BSS techniques estimate the set of components that originated the recorded brain activity blindly [28]. It should be noted that the BSS components are not equivalent generator dipoles, but mutually independent and simultaneous electromagnetic activity measured over the scalp [29,33]. In the last years, BSS algorithms have been increasingly applied to EEG and MEG data in order to isolate the artefacts that usually appear in these signals [29,33–38]. Once the artefacts have been identified and detached, the brain components are projected back to the channels to obtain the clean recordings [34,38]. On the other hand, the approach taken in this study is different. We did not aim to remove artefacts from MEG recordings with minimal brain activity distortion. Instead, we attempted to emphasise the differences between AD patients and control subjects' MEG recordings by retaining only the components which account for the most relevant

differences between groups. Thus, the partially reconstructed MEG recordings do not reflect the brain activity accurately, but they should have more different values of f_{median} and $SpecEn$ than the MEG data without BSS.

Moreover, it is worth noting that, previously to the BSS, the MEG epochs with clear artefacts were rejected. We applied the epoch rejection method in order to avoid surplus complexity and to assess the classification improvement without any other kind of preprocessing. Moreover, the same artefact-free raw MEG recordings were used to compute the f_{median} and $SpecEn$ with and without the BSS and component selection procedure. Therefore, the diverse classification results could be directly compared to evaluate the relative classification improvement.

There is a wide range of BSS algorithms that can be applied to decompose EEGs or MEGs [29]. Among these, we employed AMUSE [27,36,42], which is based on second order statistics [29] likewise other BSS algorithms, such as the second order blind identification (SOBI) algorithm [28,32]. SOBI minimises the cross-correlations at a much denser set of time delays than AMUSE [32]. Although AMUSE might not separate the components as completely as SOBI [32], the computational complexity of AMUSE is lower than in most BSS algorithms [36]. Furthermore, AMUSE has other advantages: it always offers the same separation when applied to the same input data set and orders the components by decreasing linear predictability [27,42]. This inherent order is one of the key points of this component selection procedure, since it enables us to straightforwardly compare AMUSE components from different epochs and subjects. On the other hand, due to the fact that AMUSE only uses two time delays to decorrelate the signals, the AMUSE decomposition may be less robust to

additive white noise than that computed using SOBI or other BSS algorithms [32,36]. Nevertheless, the simplicity of AMUSE makes the interpretation of the component order in terms of f_{median} or *SpecEn* plain.

The features used for classification were f_{median} and *SpecEn*. Both variables try to characterise the whole spectrum with a single value. The former assesses the slowing of the *PSD* [16], whereas the latter measures the flatness of the spectrum [19]. Moreover, both f_{median} and *SpecEn* have already been applied to the analysis of AD patients' EEG and MEG data. Our results were in agreement with these previous studies [13–17]. Firstly, the f_{median} values were lower for AD patients than for control subjects in both AMUSE components and MEG channels. This slowing was also found when different frequency bands and severity degrees of AD were analysed [11,13,14]. Secondly, AD patients had lower *SpecEn* than control subjects. This suggests that the AD patients' brain activity is more regular than in control subjects. This result was also found in EEG [17] and MEG data [16], although the differences between both groups were not significant in the EEG study. Moreover, other non-linear analysis methods support the hypothesis of decreased irregularity and complexity in AD patients' EEGs and MEGs [5,6,17,20,22–24]. Nevertheless, the origin of these changes is not yet clear, due to the heterogeneity of AD [1,5].

The Mann-Whitney U-test showed that the differences between both groups were more significant for f_{median} than for *SpecEn*. These results agree with a previous study where these variables were applied to MEG recordings [16]. Nevertheless, the *p*-values evolved in a similar way with the AMUSE index for both f_{median} and *SpecEn*. Furthermore, the most significant components were gathered together. Inspecting the *p*-values, we could

evaluate the ability of every AMUSE component to distinguish AD patients from control subjects. We decided to keep the subsets BSS- $\{15,35\}$ (21 components) and BSS- $\{20,30\}$ (11 components) to partially reconstruct the MEGs. Moreover, the projection of a component subset implies a kind of model order selection in the BSS methodology. Furthermore, we did not estimate a fixed value for n a priori to reduce the dimensionality [29]. Instead, the most significant components were projected to rebuild the recordings. In addition, we classified the subjects using the average value of f_{median} or $SpecEn$ for the 148 MEG channels.

Whereas the significance of each component was evaluated with a Mann-Whitney U-test, the classification rate improvement was measured using a ROC analysis with a leave-one-out cross-validation process. We found that the BSS and component selection procedure provided an accuracy improvement between 9.52% and 14.28%. Additionally, this procedure also increased the correlation between the MMSE scores and the average values of f_{median} and $SpecEn$ slightly. This suggests that the partial reconstruction of MEG recordings may increase the concordance between the severity of the mental impairments described by MMSE and the f_{median} and $SpecEn$ values.

A previous study where a subset of five AMUSE components extracted from 21 EEG channels were retained reported maximum accuracy improvements of 10% [27]. They tried to classify 22 MCI patients who later proceeded to AD against 38 control subjects. Our selection of the subsets BSS- $\{15,35\}$ and BSS- $\{20,30\}$ contrasts with their division [27], since in that previous work only the components below a certain index were taken into account for projection. Nevertheless, observing the p -values plotted in Fig. 3, it is clear that our first components provided little differentiation

between groups. Thus, as it was also suggested in [27], retaining an intermediate component subset, rather than just selecting the first AMUSE components, was beneficial in our case. A linear discriminant analysis with a cross-validation procedure applied to the relative power in six frequency bands was used to classify the 22 MCI patients and the 38 control subjects in [27]. Thus, the settings of that study are different from ours, as a more elaborated classification rule was used to distinguish the MCI patients. Nevertheless, that research work did not measure the improvement in each variable separately [27]. In contrast, our straightforward classification method helps to assess the improvement in each variable, f_{median} or $SpecEn$. However, both studies have reported a promising accuracy increase of about 10%. In addition, a later study used the partially reconstructed EEGs obtained in [27] to further improve the classification of the MCI patients [40]. This subsequent study achieved an additional raise of about 13% over the accuracy reported in [27] using a “bump modelling” of the EEG wavelet time-frequency transform and a neural network classifier [40]. Therefore, it can be seen that the component selection procedure not only improves the results of simple classification methods, but it also may provide high classification rates when complex discriminant techniques are used.

This procedure based on BSS and subsequent partial reconstruction of the electromagnetic brain recordings has been tested using only spectral and time-frequency features [27,40]. Nevertheless, this component selection procedure could also be applied when the brain activity is characterised with other kinds of measures, such as complexity or connectivity estimators. Non-linear complexity parameters may complement the information provided by spectral features about the brain signals [5,6].

Abnormal patterns have been found in AD patients' EEGs and MEGs with different complexity estimators [21–23]. Additionally, since AD is thought to be a syndrome of neocortical disconnection [5,6], connectivity measures may reflect an impairment of functional connectivity among cortical areas [24,25]. Consequently, future research should assess whether these or other measures could be suitably introduced into the component selection procedure. Additionally, it should be studied whether the subset of components with significant differences between AD patients and controls changes when different features are used to characterise the signals. These studies might contribute to help in clinical AD diagnosis and to increase our insight into this dementia.

Certain limitations of our study merit attention. Firstly, the sample size was small. In addition, other mental diseases, such as MCI [13,15] or other types of dementia [10,14], can produce a similar slowing in the brain activity. Thus, additional analyses with a larger database including MEG recordings from patients with other mental diseases should be carried out to confirm our results. Secondly, although the epochs used in this study have a length similar to that analysed in previous works [27,36], it should be evaluated if different epoch lengths affect the performance of our methodology. Finally, due to the simplicity of the BSS algorithm and the spectral features studied, the classification performance might be further improved using other BSS algorithms to decompose the recordings or features to characterise them.

In summary, this paper proposes a method to improve the classification of AD patients and control subjects when MEG background activity recordings are analysed. This method is based on a simple BSS algorithm –

AMUSE – [42] which orders the extracted components by decreasing linear predictability [27]. Afterwards, the components which may offer a significant differentiation between subject groups are projected back to the MEG channels, and these partially reconstructed signals are characterised with f_{median} [16] and $SpecEn$ [18,19]. The improvement in the classification performance was compared to the case where no BSS preprocessing was applied to the same MEG signals. Although this methodology must be applied to a larger database in order to validate our preliminary findings, the results showed that the classification accuracy increased between 9.52% and 14.28%, suggesting the possible usefulness of this approach to help in the AD diagnosis.

Conflict of interest

Authors have no conflicts of interest that could inappropriately influence this research work.

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Table captions

Table 1 Results from the ROC analysis with a leave-one-out cross-validation procedure for the average f_{median} values

	Without BSS	BSS- $\{15,35\}$	BSS- $\{20,30\}$
Control subjects (mean \pm SD)	13.08 \pm 2.95 Hz	12.60 \pm 1.32 Hz	12.57 \pm 1.24 Hz
AD patients (mean \pm SD)	8.98 \pm 2.32 Hz	9.76 \pm 1.69 Hz	9.83 \pm 1.71 Hz
Sensitivity (%)	71.43	85.71	80.95
Specificity (%)	66.67	80.95	80.95
Accuracy (%)	69.05	83.33	80.95

Table 2 Results from the ROC analysis with a leave-one-out cross-validation procedure for the average $SpecEn$ values

	Without BSS	BSS- $\{15,35\}$	BSS- $\{20,30\}$
Control subjects (mean \pm SD)	0.9346 \pm 0.0281	0.9549 \pm 0.0127	0.9585 \pm 0.0111
AD patients (mean \pm SD)	0.8962 \pm 0.0539	0.9303 \pm 0.0203	0.9351 \pm 0.0189
Sensitivity (%)	66.67	80.95	76.19
Specificity (%)	57.14	61.91	71.43
Accuracy (%)	61.91	71.43	73.81

Table 3 Spearman's rank correlation coefficients (ρ) between the MMSE scores and the average values of f_{median} and $SpecEn$ for each case: "Without BSS", "BSS- $\{15,35\}$ " and "BSS- $\{20,30\}$ "

	Without BSS		BSS- $\{15,35\}$		BSS- $\{20,30\}$	
	f_{median}	$SpecEn$	f_{median}	$SpecEn$	f_{median}	$SpecEn$
ρ	0.5414*	0.3933*	0.6176*	0.4934*	0.6068*	0.5485*

* Correlation was significant (p -value < 0.01).

Figure captions

Figure 1 Average f_{median} values of every AMUSE component for AD patients and control subjects.

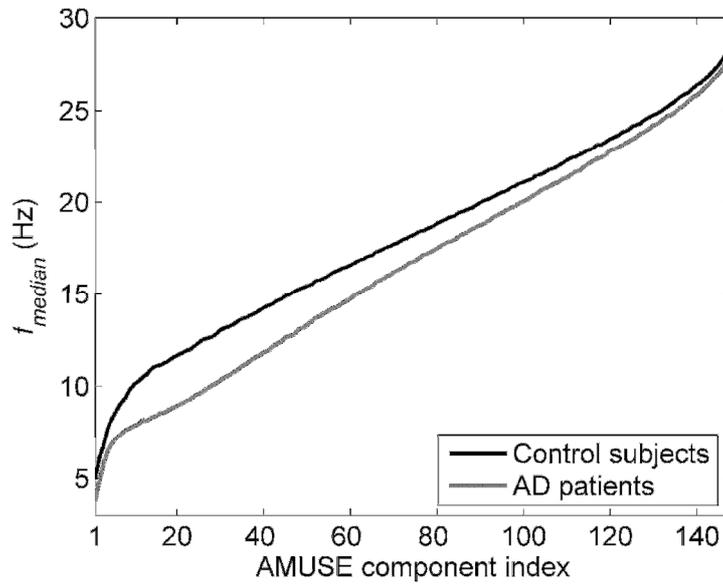


Figure 2 Average $SpecEn$ values of every AMUSE component for AD patients and control subjects.

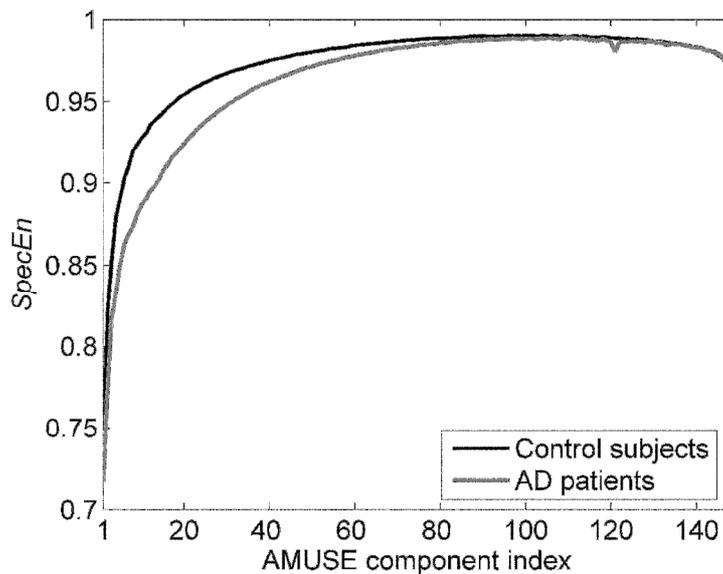


Figure 3 Bonferroni-corrected p -values of f_{median} and $SpecEn$ for every AMUSE component.

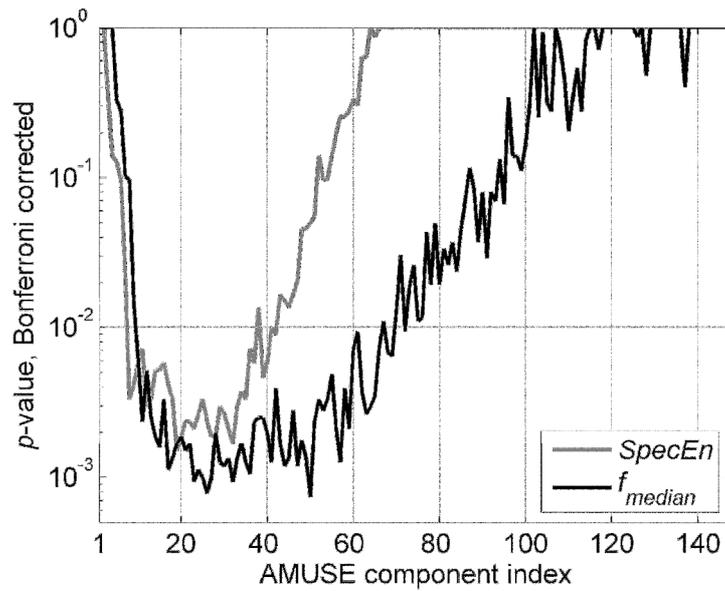


Figure 4 ROC curves computed with a leave-one-out cross-validation procedure for AD patients versus control subjects classification with f_{median} . The comparison between MEG epochs with and without the BSS component selection procedure is shown.

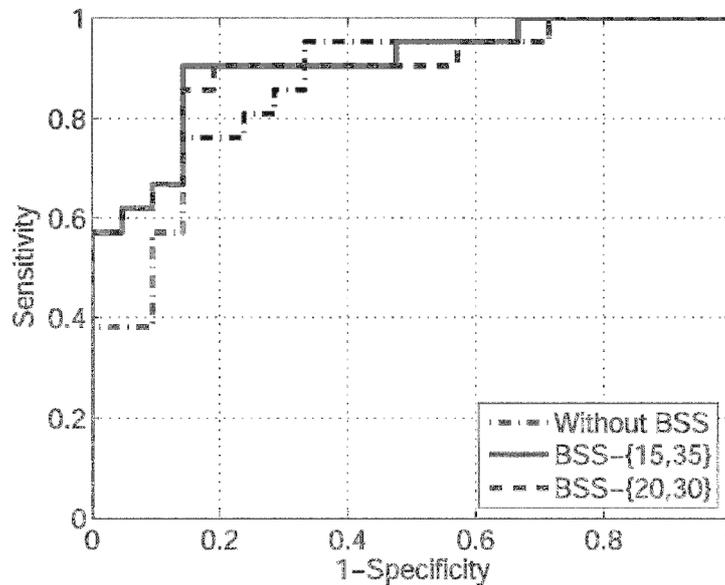


Figure 5 ROC curves computed with a leave-one-out cross-validation procedure for AD patients versus control subjects classification with *SpecEn*.

The comparison between MEG epochs with and without the BSS component selection procedure is shown.

