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Technical note

Blind source separation to enhance spectral and non-linear features of magnetoencephalogram recordings. Application to Alzheimer's disease

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ABSTRACT

This work studied whether a blind source separation (BSS) and component selection procedure could increase the differences between Alzheimer's disease (AD) patients and control subjects' spectral and non-linear features of magnetoencephalogram (MEG) recordings. MEGs were acquired with a 148-channel whole-head magnetometer from 62 subjects (36 AD patients and 26 controls), who were divided randomly into training and test sets. MEGs were decomposed using the algorithm for multiple unknown signals extraction (AMUSE). The extracted AMUSE components were characterised with two spectral – median frequency and spectral entropy (*SpecEn*) – and two non-linear features: Lempel-Ziv complexity (*LZC*) and sample entropy (*SampEn*). One-way analysis of variance with age as a covariate was applied to the training set to decide which components had the most significant differences between groups. Then, partial reconstructions of the MEGs were computed with these significant components. In the test set, the accuracy and area under the ROC curve (AUC) associated with each partial reconstruction of the MEGs were compared with the case where no BSS-preprocessing was applied. This preprocessing increased the AUCs between 0.013 and 0.227, while the accuracy for *SpecEn*, *LZC* and *SampEn* rose between 6.4% and 22.6%, improving the separation between AD patients and control subjects.

1. Introduction

Magnetoencephalogram (MEG) signals reflect the brain magnetic fields non-invasively [1]. This recording is closely related to the commonly used electroencephalogram (EEG) [1]. Although MEG equipment is more complex and expensive than EEG systems, the acquisition of the brain magnetic fields has some advantages over the EEG. For example, MEG signals are independent of any reference point. Additionally, they are less affected by extracerebral tissues than the EEG [1]. Thus, MEG can be useful to explore both normal and abnormal brain activities [1], such as the alterations caused by Alzheimer's disease (AD).

AD is the most common neurodegenerative disorder among elderly people in western countries [2]. It causes a progressive and irreparable impairment of mental functions which leads to the patient's death [2,3]. Moreover, AD diagnosis largely depends on the exclusion of other dementias and it can only be confirmed by necropsy [2,3]. Due to the fact that AD affects the brain cortex and that the EEG and MEG reflect brain cortical activity, the usefulness of these recordings to help in the diagnosis of this dementia has been extensively researched in the last decades [3,4].

EEG and MEG have been analysed with several signal processing techniques to gain insight into AD [3–5]. For instance, spectral features have been used to quantify the abnormalities in the spectra of AD patients' EEGs and MEGs [3,6–8]. Additionally, non-linear analysis methods can provide useful information about the brain dynamics in this dementia [4,5,8–10]. Nevertheless, it is desirable to develop novel strategies to help in AD detection from the analysis of the electromagnetic brain activity [9,11,12]. Techniques based on spatial filtering can help to achieve this goal, as these algorithms offer additional perspectives to examine EEG and MEG signals [11–14]. For instance, common spatial patterns (CSP) have been recently applied to enhance characteristics of EEG recordings in mild cognitive impairment (MCI) patients who eventually developed AD [11].

Another kind of spatial filtering techniques is blind source separation (BSS) [15,16]. BSS methods estimate the underlying components of the EEG and MEG signals without a priori information about those components (i.e., the components themselves and the process that produced the observed recordings are unknown) [15–17]. Since these techniques isolate specific physiological activities into different components, they have been used to reject artefacts [16–19]. This application is based on the fact that BSS isolates the artefacts into a few components. Then,

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the brain recordings are reconstructed without the artefactual components [18,19]. EEG and MEG data can also be processed with BSS methods to help in the recognition of neurological disorders. For example, BSS can separate specific brain activity related to epilepsy [20] or the Creutzfeldt–Jakob disease [21]. Considering these research studies, it can be hypothesised that the application of BBS, together with features extracted from electromagnetic brain activity recordings, may enhance features associated with diseases like AD. This is due to the fact that some BSS components of the EEG and MEG signals may be more sensitive to AD than others [12,14,22]. Hence, the most relevant components may be selected and the electromagnetic brain signals may be partially reconstructed using only these components to achieve a better discrimination between AD patients and healthy subjects [14].

In this work, we wanted to evaluate whether a BSS preprocessing might enhance the separation between AD patients and elderly control subjects based on spectral and non-linear features of MEG signals. Additionally, we aimed at determining whether the range of BSS components with significant differences between demented patients and controls differed when both kinds of features (spectral and non-linear ones) were considered. We also intended to confirm the results of a previous pilot study [14].

2. Subjects and magnetoencephalogram recordings

MEG recordings were acquired from 62 subjects: 36 AD patients (24 women and 12 men) and 26 elderly control subjects (17 women and 9 men). All patients were recruited from the "Asociación de Enfermos de Alzheimer" (Spain) and fulfilled the criteria of probable AD according to the guidelines of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [23]. Brain scans and thorough medical, physical, neurological, psychiatric and neurophysiological examinations were performed to diagnose the dementia. No patient was receiving medication that could affect the MEG. The control group consisted of elderly control subjects without past or present neurological disorders. Table 1 shows the mean and standard deviation (SD) of the age and mini-mental state examination (MMSE) score [24] for all AD patients and control subjects. It is worth noting that the difference in age between groups was not significant (p-value = 0.1911, Student's t-test). All control subjects and AD patients' caregivers gave their informed consent to participate in the study, which was approved by the local ethics committee.

Table 1
Demographic and clinical features for all participants, and the training and test sets. Data are given as mean ± SD.

	All subjects	
	AD patients	Control subjects
Number of subjects	36	26
Number of females	24	17
Age (years)	74.06 ± 6.95	71.77 ± 6.38
MMSE score	18.06 ± 3.36	28.88 ± 1.18
	Training set	
	AD patients	Control subjects
Number of subjects	18	13
Number of females	12	9
Age (years)	74.11 ± 7.38	71.38 ± 4.84
MMSE score	17.72 ± 3.63	28.92 ± 1.04
	Test set	
	AD patients	Control subjects
Number of subjects	18	13
Number of females	12	8
Age (years)	74.00 ± 6.70	72.15 ± 7.82
MMSE score	18.39 ± 3.15	28.85 ± 1.34

The population was divided randomly into a training set (18 AD patients and 13 control subjects) and a test set (formed by other 18 demented patients and 13 controls). The training set was used to develop the BSS preprocessing and to find the classification rules for each case. Then, these algorithms were applied, without further modification, to the test set to independently assess the improvement in the separation between AD patients and control subjects due to the BSS preprocessing. The demographic data and clinical features of training and test sets are also summarized in Table 1.

MEG signals were acquired with a 148-channel whole-head magnetometer (MAGNES 2500 WH, 4D Neuroimaging) placed in a magnetically shielded room at the "Centro de Magnetoencefalografía Dr. Pérez-Modrego" (Spain). Five minutes of MEG were recorded from each of the subjects while they lay on a patient bed in a relaxed state, awake and with eyes closed. The sampling frequency was 678.19 Hz. To reduce data length, the recordings were decimated to 169.55 Hz. This procedure consisted of filtering the MEGs according to the Nyquist criterion and down-sampling them by a factor of four. For each subject, an average number of 17.60 ± 6.23 epochs (mean ± SD) of 10 s (1695 samples) that were simultaneously artefact-free at all channels were selected for analysis. Finally, signals were digitally filtered between 1.5 and 40 Hz.

3. Methods

Our methodology is introduced in the following lines. In order to test the BSS preprocessing on completely unseen data, the selection of the most sensitive components to AD was performed using the training set, whereas the assessment of the improvement in the separation between AD patients and controls was carried out with the test set. Firstly, a BSS algorithm was applied to extract the components from the MEG recordings orderly. Secondly, two spectral and two non-linear analysis methods were applied to every BSS component in the training set. For each of these four features, different ranges of components that accounted for the most significant differences between the demented patients and controls were selected to partially reconstruct the MEG signals. Afterwards, the four metrics were applied to the partially reconstructed MEG signals and to the original recordings (without the BSS preprocessing) of the training set. Subject classification rules were then derived using linear discriminant analysis (LDA). Finally, these classification thresholds for the original MEG recordings and the BSS preprocessed signals were applied to the test set in order to evaluate the enhancement in the separation between AD patients and controls due to the BSS and component selection procedure.

3.1. Blind source separation (BSS) algorithm

BSS techniques estimate the set of n unknown components, $\mathbf{s}(t) = [s_1(t), \ldots, s_n(t)]^T$, where ^{T} denotes transposition, which were linearly mixed by the full rank $m \times n$ matrix $\mathbf{A}$ ($m \geq n$) to form m temporally and spatially correlated recordings, $\mathbf{x}(t) = [x_1(t), \ldots, x_m(t)]^T$ [15,16]. Here, $\mathbf{x}(t)$ represents the MEGs, which are related to $\mathbf{s}(t)$ by:

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

where $\mathbf{x}(t)$ and $\mathbf{s}(t)$ are supposed to have zero mean.

Several assumptions are needed to estimate $\mathbf{s}(t)$ and $\mathbf{A}$ from $\mathbf{x}(t)$ [16,17]. The most important one is that the components are mutually independent or, alternatively, that they should be decorrelated at any time delay. Additionally, the mixing process should be linear and instantaneous. It has been proven that EEG and MEG data fulfil these hypotheses [16,17]. For simplicity, we assume that $m = n$ thanks to the fact that only the most relevant components will be