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Research report

Multiscale entropy analysis of resting-state magnetoencephalogram with tensor factorisations in Alzheimer's disease

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ABSTRACT

Tensor factorisations have proven useful to model amplitude and spectral information of brain recordings. Here, we assess the usefulness of tensor factorisations in the multiway analysis of other brain signal features in the context of complexity measures recently proposed to inspect multiscale dynamics. We consider the "refined composite multiscale entropy" (*rcMSE*), which computes entropy "profiles" showing levels of physiological complexity over temporal scales for individual signals. We compute the *rcMSE* of resting-state magnetoencephalogram (MEG) recordings from 36 patients with Alzheimer's disease and 26 control subjects. Instead of traditional simple visual examinations, we organise the entropy profiles as a three-way tensor to inspect relationships across temporal and spatial scales and subjects with multiway data analysis techniques based on PARAFAC and PARAFAC2 factorisations. A PARAFAC2 model with two factors was appropriate to account for the interactions in the entropy tensor between temporal scales and MEG channels for all subjects. Moreover, the PARAFAC2 factors had information related to the subjects' diagnosis, achieving a cross-validated area under the ROC curve of 0.77. This confirms the suitability of tensor factorisations to represent electrophysiological brain data efficiently despite the unsupervised nature of these techniques.

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1. Introduction

The electroencephalogram (EEG) and magnetoencephalogram (MEG) are non-invasive neurophysiological recordings of the small electromagnetic fields generated by the neurons. Both EEG and MEG are direct measures of the neural activity and they have excellent temporal resolution (Lopes da Silva, 2013). The transient temporal fluctuations in the EEG and MEG signals reflect the signal variability, which conveys information about the brain (Heisz and McIntosh, 2013; Lopes da Silva, 2013; Stam, 2005). Among the variety of techniques useful to assess such variability, the evaluation of relationships across multiple temporal scales has recently sparked interest in the field (Escudero, 2015; Heisz and McIntosh, 2013; McDonough and Nashiro, 2014; Morabito et al., 2012).

Such interest is motivated by the fact that the presence of temporal relationships over short and long scales is an inherent part of physiological signals and it is essential for the evaluation of physiological complexity (Costa et al., 2002; Goldberger et al., 2002), a topic with implications in both diagnosis support and the evaluation of dynamical models of biological systems (Costa et al., 2005, 2002; Escudero, 2015). Loss of complexity is often related to ageing and/or pathological conditions because it may reflect decreased ability to adapt to an ever-changing environment (Ahmed and Mandic, 2011; Costa et al., 2005, 2002; Goldberger et al., 2002; Tononi and Edelman, 1998; Yang and Tsai, 2013).

Multiscale entropy (*MSE*) is a signal complexity metric that inspects relationships across multiple temporal scales (Costa et al., 2005, 2002). The ability of the *MSE* to characterise brain dynamics in EEG and MEG signals has been demonstrated in several conditions (Bosl et al., 2011; Catarino et al., 2011; Chung et al., 2013; Escudero et al., 2006; Heisz and McIntosh, 2013; Takahashi et al., 2010; Yang et al., 2013). The *MSE* algorithm has recently been improved in terms of accuracy and validity over long scales

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(Wu et al., 2013, 2014), leading to the so-called refined composite *MSE* (*rcMSE*). However, both *MSE* and *rcMSE* are applied to single channel recordings. Moreover, the entropy "profiles" resulting from different channels are compared only visually. This is in contrast with the fact that complex dynamics may lead to structure on both multiple spatial and temporal scales and it shows the need for data-driven approaches to inspect potential relationships over several channels and temporal scales across different subjects.

Significant efforts have been devoted to finding efficient data-driven representations of electrophysiological brain data (Miwakeichi et al., 2004). Common methods rely on representing the data at hand in the form of a matrix (two-way array) and then factorising it (using, for example, principal component analysis – PCA – or independent component analysis – ICA). However, an intrinsic problem of these representations is that the factorisations defined by only two modes (i.e., rows and columns in matrices that represent, for example, space and time) are not uniquely determined: additional constraints are needed to make them unique (Acar and Yener, 2009; Miwakeichi et al., 2004; Möcks, 1988; Mørup et al., 2006). In PCA, orthogonality between components is imposed. ICA uses an even stronger constraint: statistical independence (Miwakeichi et al., 2004). These a priori assumptions are not fully realistic from a physiological point of view for neuroscience data (De Vos et al., 2007; Miwakeichi et al., 2004; Mørup et al., 2006).

Matrices may provide a too limited representation of the information captured in brain research experiments, where often temporal data coming from several subjects, channels, etc. needs to be jointly analysed (Acar and Yener, 2009). A powerful alternative is to maintain the naturally occurring N-way (with $N \geq 3$) structure of the data intact and to consider multiway data analysis techniques. This refers to the extension of two-way techniques to N-way data arrays (i.e., higher-order tensors) (Acar and Yener, 2009). Working with higher-order tensors has the major advantage that unique multi-linear factorisations can be achieved under fairly mild conditions, meaning that we are able to estimate the latent components that gave rise to the data (Cichocki et al., 2015; Kolda and Bader, 2009; Miwakeichi et al., 2004; Möcks, 1988; Mørup, 2011). Indeed, tensor arrays occur naturally in various settings of brain research and they can often be factorised as a sum of factors, each of which is the product of the components in each way (Miwakeichi et al., 2004).

Seminal studies introduced multiway factorisations (particularly parallel factor analysis – PARAFAC, see Section 3.3.1) in the analysis of EEG event-related potentials (ERPs) (Cole and Ray, 1985; Möcks, 1988). Miwakeichi et al. (2004) further illustrated the use of PARAFAC to compute a tri-linear decomposition of a time-frequency representation of EEG signals in different cognitive states. More recent studies used these approaches for artefact recognition in brain recordings (Acar et al., 2007). The use of PARAFAC has also been demonstrated in tensor factorisations of ERPs with $N > 3$ (e.g., $N = 5$ with modes: channel × frequency × time × subject × condition) (Mørup et al., 2006). Epilepsy has been a prolific field of research for tensor factorisations of brain features, including the detection of seizure onset zone (Acar et al., 2007; De Vos et al., 2007). Multiway array decompositions have also been applied to spectral characteristics of EEG signals in dementia (Latchoumane et al., 2012). Overall, PARAFAC, one of the simplest tensor factorisation methods, has been the dominant technique in the literature despite other models being potentially more appropriate for some brain research experiments (Cichocki et al., 2015; Mørup et al., 2008).

Here, we illustrate the potential of tensor factorisations for electrophysiological data analysis to the wider community by proposing a data-driven tensor factorisation of *rcMSE* features computed from MEG signals of Alzheimer's disease (AD) patients and control (CON) subjects. We report: (1) the first application of *rcMSE* to brain activity; (2) a data-driven description of multiscale MEG features based on multiway array decompositions; and (3) the classification of unseen subjects using the factors computed via the multiway array decomposition, which is an unsupervised technique.

Our choice of AD is motivated by the fact that it is the most common neurodegenerative disease in western societies. The number of people suffering from AD is expected to double approximately every 20 years (Wimo and Prince, 2010). The onset of AD occurs years before the first clinical symptoms appear and a definite diagnosis can only be achieved with a necropsy (McKhann et al., 2011). Thus, diverse signal features are being investigated to monitor the alterations that AD causes in resting-state brain activity (Hornero et al., 2009; Stam, 2005).

2. Materials

Resting-state MEG activity was recorded from 36 AD patients and 26 healthy age-matched CON subjects. All participants gave their informed consent for the research, which was approved by the local ethics committee. Exhaustive medical, neurological, psychiatric, neuroimaging, and neuropsychological tests were used to confirm the clinical diagnoses. The Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and the Global Deterioration Scale/Functional Assessment Staging (GDS/FAST) (Rosen et al., 1984) were used to screen their cognitive and functional status, respectively.

The 36 AD patients (24 females) met the criteria for probable AD according to NINCDS–ADRDA guidelines (McKhann et al., 1984). Their mean age, MMSE and GDS/FAST scores were 74.06 ± 6.95 years, 18.06 ± 3.36, and 4.17 ± 0.45, in that order (data given as mean ± standard deviation, SD). The 26 CON subjects (17 females) were 71.77 ± 6.38 years old (mean ± SD). Their MMSE and GDS/FAST scores were 28.88 ± 1.18 and 1.73 ± 0.45 (mean ± SD), respectively. The difference in age between groups was not significant (p-value = 0.1911, Student's t-test). All subjects were free of significant neurological and psychiatric diseases other than AD and were not taking medication that could affect the MEG activity.

The MEGs were acquired in a magnetically shielded room with a 148-channel whole-head magnetometer (MAGNES 2500 WH, 4D neuroimaging) at the MEG Centre Dr. Pérez-Modrego (Complutense University of Madrid, Spain). The MEG activity was recorded while the subjects were lying on a patient bed with eyes closed and in a relaxed state. They were asked to stay awake and not to move eyes and head. For each participant, MEG background activity was recorded for 5 min at 678.19 Hz with a 0.1–200 Hz hardware bandpass filter. The MEG equipment decimated each 5-min dataset by a factor of four using a second-order Butterworth IIR anti-aliasing filter, applied in both forward and reverse directions, with cut-off frequency at 76.30 Hz (45% of the final sampling frequency: $f_s = 169.55$ Hz). Epochs of 10 s (1695 samples) with minimal ocular artefacts were selected for analysis. Finally, a notch filter at the power line frequency (50 Hz) and an FIR bandpass filter between 1 Hz and 60 Hz were applied to the MEG epochs.

3. Methodology

The description of our methodology starts with the explanation of the *rcMSE* (Wu et al., 2014). For a unidimensional signal, the *rcMSE* computes levels of entropy for several temporal scales. Afterwards, we will describe how to take advantage of the multiway linkages in our data by building an 'entropy tensor' with modes MEG channels × temporal scales × subjects. The PARAFAC (Carroll and Chang, 1970; Harshman, 1970) and PARAFAC2