Regularity Analysis of the Magnetoencephalogram Background Activity in Alzheimer's Disease Patients Using Auto Mutual Information

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INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia (Bird, 2001), a group of conditions that gradually destroys brain cells and leads to progressive decline in mental function. This irreversible brain disorder is characterized by neuronal loss and the appearance of neuritic plaques containing amyloid-β-peptide and neurofibrillary tangles (Cummings, Pike, Shankle, & Cotman, 1996). Approximately 50–60% of patients with dementia over 65 years are clinically related to AD and the number of patients is expected to increase continuously (Lahiri, Farlow, Greig, & Sambamurti, 2002). A differential diagnosis with other types of dementia and with major depression is used. It can include Mini-Mental Statues Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), magnetic resonance imaging, computerized axial tomography, positron emission tomography, and verbal tests. Nevertheless, a definite diagnosis of AD is only possible by necropsy. In order to complete the diagnosis, nonlinear analysis of the brain recordings might be used.

Magnetoencephalograpy (MEG) is a noninvasive technique that allows recording the magnetic fields produced by brain activity. SQUID (Superconducting QUantum Interference Device) sensors immersed in liquid helium at 4.2 K are used to detect the extremely weak brain magnetic signals. MEG provides an excellent temporal resolution, orders of magnitude better than in other methods for measuring cerebral activity, as magnetic resonance imaging, single-photon-emission computed tomography and positron-emission tomography (Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993). A good spatial resolution is also provided, although this depends on the source configuration (Hari & Forss, 1999). Moreover, this technique is independent of any reference point. In addition, magnetic fields are not distorted by the resistive properties of the skull (Hämäläinen et al., 1993). Nevertheless, the recordings are very sensitive to external artifacts. Thus, the signals must be acquired in a magnetically shielded room.

In this preliminary study, we examined the MEG background activity in patients with probable AD, and in age-matched control subjects using auto mutual information (AMI). Our purpose is to test the hypothesis that an abnormal type of nonlinear dynamics is associated with AD.

BACKGROUND

In the last years, brain activity of AD patients has been analyzed with several nonlinear methods. The most widely used are the correlation dimension (D_2) and the first Lyapunov exponent (L_1). D_2 is a measure of the system dimensional complexity (Grassberger & Procaccia, 1893a, 1893b) while L_1 is a dynamic complexity measure that describes the divergence of trajectories starting at nearby initial states (Jeong, 2004). Jeong, Kim, and Han (1998) showed that AD patients' EEGs exhibit significantly lower D_2 and L_1 than the EEGs of control subjects in many channels. Van Cappellen van Walsum, Pijnenburg, Berendse, van Dijk, Know, Scheltens, and Stam (2003) used MEG data and computed the D_2 in different frequency bands. In the broad band 0.5–40 Hz, the mean D_2 was lower in AD patients compared with control subjects. Nevertheless, there are

several drawbacks in using these nonlinear methods. Reliable estimations of D_2 and L_1 require a large quantity of data (Eckmann & Ruelle, 1992), and stationary and noise-free time series (Grassberger & Procaccia, 1983a). These assumptions cannot be achieved for physiological data. Moreover, the computational cost is high, especially for great amount of data.

Therefore, other nonlinear methods which avoid these disadvantages are necessary to study the MEG background activity. Lempel-Ziv complexity measures the complexity of finite sequences, and is related to the number of distinct substrings and the rate of their occurrence along the sequence (Lempel & Ziv, 1976). Recent studies have applied this nonlinear method to EEG (Abásolo, Hornero, Gómez, García, & López, 2006b) and MEG signals (Gómez, Hornero, Abásolo, Fernández, & López, 2006) of AD patients and elderly control subjects, finding significant differences between both groups in certain regions of the brain. Other methods measure the irregularity of a signal, as the approximate entropy and the sample entropy. With both methods, an increased regularity was found in the EEG of AD patients (Abásolo, Hornero, Espino, Álvarez, & Poza, 2006a; Abásolo, Hornero, Espino, Poza, Sánchez, & de la Rosa, 2005). Finally, the interdependencies between MEG signals in six frequency bands were studied with synchronization likelihood (Stam, Jones, Manshanden, van Cappellen van Walsum, Montez, Verbunt, de Munck, van Dijk, Berendse, & Scheltens, 2006).

In this study, another nonlinear method, the auto mutual information (AMI), has been used to analyze the MEG signals. Mutual information (MI) has been used to study different types of diseases and brain states. It has been shown that MI might be useful to predict the response to anesthesia (Huang, Yu, Ju, & Cheng, 2003). Xu, Liu, Liu, and Yang (1997) computed the complexity of cross-mutual information (CMI) functions among eight EEG channels for four different functional states: awake with opened and closed eyes, light sleep, and deep sleep. Na, Jin, Kim, and Ham (2002) estimated the decreased rate of AMI and the CMI values from the EEG of ten schizophrenic patients and ten normal controls. Both nonlinear methods were also applied to study the EEG activity in AD (Jeong, Gore, & Peterson, 2001a). They found that AMI profiles decreased more slowly with time delay throughout the brain in AD patients than in control subjects. The CMI analyses showed a

significantly decreased transmission of information between pairs of AD patients' electrodes.

MATERIALS AND METHODS

Subjects and MEG Recording

MEG signals were recorded with a 148-channel whole head magnetometer (MAGNES 2500 WH, 4D Neuroimaging) in a magnetically shielded room. The subjects lay on a patient bed, in a relaxed state, and with their eyes closed. Five minutes of recording were acquired at a sampling frequency of 678.17 Hz. Then, these recordings were down-sampled to 169.549 Hz. Artifact-free epochs of 20 seconds (3392 data points) were selected and filtered with a band-pass filter (0.5-40 Hz).

The MEG data were acquired from 30 subjects. 15 patients (three men and 12 women) fulfilling the criteria of probable AD (age = 71.13 ± 8.52 years, mean ± standard deviation SD) participated in the present study. All of them were recruited from the Asociación de Familiares de Enfermos de Alzheimer (AFAL). The patients were diagnosed according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association (NINCDS-ADRDA) (McKhann, Drachman, & Folstein, 1984). Functional assessment staging procedure (FAST) was used for assessment of functional ability and MMSE for measuring the cognitive status of the subjects. The MMSE and FAST scores were 18.07 ± 4.18 and 4.00 ± 0.38 (mean ± SD), respectively. None of the patients used any kind of medication that could have an influence on the MEG.

MEGs were also obtained from 15 age-matched control subjects (seven men and eight women, age = 70.73 ± 8.29 years, MMSE = 29.13 ± 0.99, FAST = 1.67 ± 0.49, mean ± SD). Sex, age, MMSE, and FAST scores of all subjects are shown in Table 1. The local ethics committee approved the study. All control subjects and all caregivers of the demented patients gave their informed consent for the participation in the current research.

Auto Mutual Information

Mutual information (MI) provides a measure of both the linear and nonlinear statistical dependencies between two time series (Jeong et al., 2001a). It can be defined

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