Biosystems & Biorobotics

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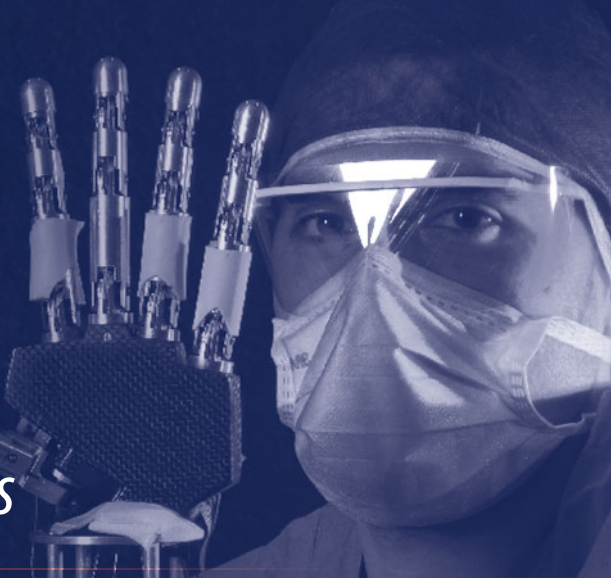

Converging Clinical and Engineering Research on Neurorehabilitation III

Proceedings of the 4th International Conference on NeuroRehabilitation (ICNR2018), October 16–20, 2018, Pisa, Italy

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Biosystems & Biorobotics

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Aims & Scope

Biosystems & Biorobotics publishes the latest research developments in three main areas: 1) understanding biological systems from a bioengineering point of view, i.e. the study of biosystems by exploiting engineering methods and tools to unveil their functioning principles and unrivalled performance; 2) design and development of biologically inspired machines and systems to be used for different purposes and in a variety of application contexts. The series welcomes contributions on novel design approaches, methods and tools as well as case studies on specific bioinspired systems; 3) design and developments of nano-, micro-, macrodevices and systems for biomedical applications, i.e. technologies that can improve modern healthcare and welfare by enabling novel solutions for prevention, diagnosis, surgery, prosthetics, rehabilitation and independent living.

On one side, the series focuses on recent methods and technologies which allow multiscale, multi-physics, high-resolution analysis and modeling of biological systems. A special emphasis on this side is given to the use of mechatronic and robotic systems as a tool for basic research in biology. On the other side, the series authoritatively reports on current theoretical and experimental challenges and developments related to the "biomechatronic" design of novel biorobotic machines. A special emphasis on this side is given to human-machine interaction and interfacing, and also to the ethical and social implications of this emerging research area, as key challenges for the acceptability and sustainability of biorobotics technology.

The main target of the series are engineers interested in biology and medicine, and specifically bioengineers and bioroboticists. Volume published in the series comprise monographs, edited volumes, lecture notes, as well as selected conference proceedings and PhD theses. The series also publishes books purposely devoted to support education in bioengineering, biomedical engineering, biomechatronics and biorobotics at graduate and post-graduate levels.

About the Cover

The cover of the book series Biosystems & Biorobotics features a robotic hand prosthesis. This looks like a natural hand and is ready to be implanted on a human amputee to help them recover their physical capabilities. This picture was chosen to represent a variety of concepts and disciplines: from the understanding of biological systems to biomechatronics, bioinspiration and biomimetics; and from the concept of human-robot and human-machine interaction to the use of robots and, more generally, of engineering techniques for biological research and in healthcare. The picture also points to the social impact of bioengineering research and to its potential for improving human health and the quality of life of all individuals, including those with special needs. The picture was taken during the LIFEHAND experimental trials run at Università Campus Bio-Medico of Rome (Italy) in 2008. The LIFEHAND project tested the ability of an amputee patient to control the Cyberhand, a robotic prosthesis developed at Scuola Superiore Sant'Anna in Pisa (Italy), using the tf-LIFE electrodes developed at the Fraunhofer Institute for Biomedical Engineering (IBMT, Germany), which were implanted in the patient's arm. The implanted tf-LIFE electrodes were shown to enable bidirectional communication (from brain to hand and vice versa) between the brain and the Cyberhand. As a result, the patient was able to control complex movements of the prosthesis, while receiving sensory feedback in the form of direct neurostimulation. For more information please visit http://www.biorobotics.it or contact the Series Editor.

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Analysis of Spontaneous EEG Activity in Alzheimer's Disease Patients by Means of Multiscale Spectral Entropy

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Abstract. The aim of this study was to analyze electroencephalographic (EEG) background activity in Alzheimer's disease (AD) and mild cognitive impairment (MCI) by means of multiscale spectral entropy (MSSE). To achieve this goal, five minutes of EEG activity were acquired from 18 cognitive healthy controls, 10 MCI subjects and 32 AD patients. Our results showed statistically significant differences (p-values < 0.05, Kruskal-Wallis test) in MSSE values for all scale factors. Additionally, a 3D receiver operating characteristic (ROC) curve was used to assess the discrimination ability of MSSE among the 3 groups, showing a good three-way discrimination power (volume under the surface of 0.6). These results suggest that MSSE can be a useful measure to characterize neural alterations in AD, even at early stages.

1 Introduction

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder with high prevalence [1]. Its symptoms include cognitive impairment, memory loss and

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attention deficit, among others. The gold standard for AD diagnosis is the histological examination of brain tissue to confirm the presence of Aβ peptide plaques and tau protein fibril tangles [2]. Mild cognitive impairment (MCI) is considered a prodromal state in AD development [3]. MCI is a crucial pathological entity for an early AD diagnosis.

Spectral entropy (SpecEn) is a measure of the disorder relying on the signal power spectrum [4]. It is widely applied to many biomedical signal processing problems. However, a single scale is often not enough to reveal the complex behavior of a physiological system [4]. Besides, AD is characterized by abnormal brain physiology behavior, which can be observed in high scales [5]. For these reasons, in our study SpecEn method was calculated from a multiscaled approach.

Multiscale spectral entropy (MSSE) quantifies irregularity patterns of the underlying system at different scales, and it may be related with its structural complexity. To the best of our knowledge, this is the first time that MSSE is applied to electroencephalographic (EEG) data in order to characterize brain dynamics in AD. This technique can show new insights to categorize AD neurodegeneration evolution. In this regard, the aim of this study is to analyze spectral components from EEG signals in order to characterize abnormal neural dynamics in AD and MCI.

2 Materials and Methods

2.1 Materials

Sixty subjects took part in the study: 18 controls with a median age of 76 (interquartile range (IQR) = [73, 82]) years, 10 mild cognitive impaired (MCI) subjects with a median age of 81.5 (IQR = [78, 87]) years and 32 AD patients with a median age of 80 (IQR = [75, 87]) years. Patients were diagnosed according to the criteria of the National Institute on Aging and Alzheimer's Association (NIA-AA).

EEG signals were recorded with a 19-channel Nihon Kohden Neurofax JE-921A EEG System, at electrodes F3, F4, F7, F8, Fp1, Fp2, T3, T4, T5, T6, C3, C4, P3, P4, O1, O2, Fz, Cz and Pz of the International 10'20 System. Sampling frequency was established to 500 Hz. Five minutes of resting state activity were acquired while the subjects stayed with their eyes closed in a noise-free environment.

Afterwards, EEG data were preprocessed according to the following steps: (i) bandpass filtering with a Hamming window between 0.4 and 98 Hz, (ii) independent component analysis (ICA), (iii) segmentation into 2 s epochs and visual rejection of epochs contaminated by artifacts.

2.2 Methods

MSSE was calculated for each artifact-free epoch. The algorithm to compute MSSE entropy is the following. Given a one-dimensional discrete time series,

$[x_1, \ldots, x_i, \ldots, x_N]$, successive coarse-grained time series $[Y^{(\tau)}]$ are built according to the scale factor τ [5]:

$$Y_j^{\tau} = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} x_i, \quad 1 \leq j \leq \frac{N}{\tau} = N^{(\tau)}, \tag{1}$$

It is important to note that for scale $\tau = 1$, $[Y^1]$, the resulting coarse-grained sequence is equal to the original sequence. The maximum analyzed scale was $\tau_{MAX} = 20$.

Afterwards, normalized PSD function is computed for each coarse-grained time series. Normalized PSD is finally used to calculate SpecEn according to the following equation [6]:

$$SpecEn = -\frac{1}{ln(N)} \sum_{f=f1}^{f2} PSDn(f) ln[PSDn(f)], \tag{2}$$

where $PSDn$ is the power spectral density of a coarse-grained sequence with frequency limits at $f1$ and $f2$. Notably, higher SpecEn values correspond to higher irregularity of the associated PSD [6].

3 Results and Discussion

MSSE was applied to the EEG data from 32 AD patients, 10 MCI subjects and 18 controls. Kruskal-Wallis test and Mann-Whitney U-test were used to determine statistical differences among the groups. Median MSSE profiles for each group, averaged for all trials and channels, are displayed in Fig. 1. Kruskal-Wallis p-values were obtained for each scale, represented on the top of Fig. 1.

This study reveals important differences in lower scales between MSSE profiles of controls and AD patients ($p\text{-}values < 0.01$ at scales 1 to 6, Mann-Whitney

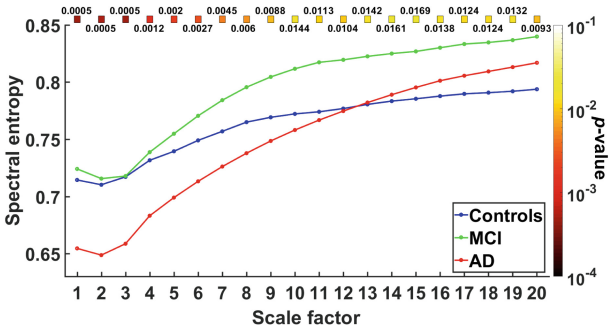

Fig. 1. Median spectral entropy values for each scale factor and each group (controls, MCI subjects and AD patients). On the top of the figure, p-values (Kruskal-Wallis test) for each scale factor are displayed.

U-test), whilst MCI subjects were indistinguishable from controls. For low scales, MSSE values were smaller in AD patients than in MCI subjects and controls. These results agree with other studies [7] that revealed a SpecEn decrease in AD patients in comparison with in controls.

MSSE exhibited an increasing tendency for each group as factor scale augmented. At higher scales, MCI patients become distinguishable from controls (p-values < 0.01 at scales between 15 and 20, Mann-Whitney U-test). This point is crucial in early AD diagnosis, as MCI often is linked with the first steps at AD neural degeneration.

In order to study the discrimination power of MSSE, a 3D receiver operating characteristic (ROC) surface was used (Fig. 2). A 3D ROC allows to express a three-way classification according to two changing discriminating thresholds. These results were applied for a scale factor of 3, since it revealed the highest volume under the surface (VUS): 0.6. For each pairwise comparison, we obtained the following values of area under the ROC curve (AUC): 0.8 for controls vs. AD comparison, 0.6 for controls vs. MCI, and 0.8 for MCI vs. AD. Since a random two-way classifier would obtain an AUC of 0.5 and a three-way classifier would obtain a VUS of 0.167 [8], we can conclude that MSSE at scale factor 3 provides a good discrimination among groups.

In summary, MSSE analysis provides a complementary point of view to other multiscale entropy studies, such as multiscale approximate entropy and multiscale sample entropy, since it evaluates the EEG in the spectral domain. Power spectrum shape is altered and the dominant frequency shifted as the AD develops to further stages [8]. Our methodology may be useful to distinguish between

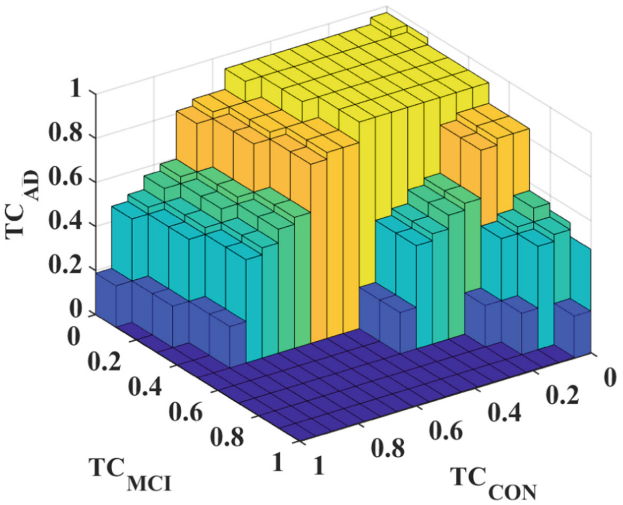

Fig. 2. 3D ROC surface (TC_{CON}: true class for controls; TC_{MCI}: true class for MCI subjects; TC_{AD}: true class for AD patients).

healthy subjects and AD patients, even in incipient stages of the disease. However, further studies with a large number of subjects are needed to confirm these results.

References

1. Hebert, L.E., et al.: Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch. Neurol. **60**(8), 1119–1122 (2003)
2. Babiloni, C., et al.: Brain neural synchronization and functional coupling in Alzheimer's disease as revealed by resting state EEG rhythms. Int. J. Psychophysiol. **103**, 88–102 (2016)
3. Petersen, R.C.: Mild cognitive impairment as a diagnostic entity. J. Intern. Med. **256**(3), 183–194 (2004)
4. Humeau-Heurtier, A., et al.: Refined multiscale Hilbert'Huang spectral entropy and its application to central and peripheral cardiovascular data. IEEE Trans. Biomed. Eng. **63**(11), 2405–2415 (2016)
5. Escudero, J., et al.: Analysis of electroencephalograms in Alzheimer's disease patients with multiscale entropy. Physiol. Meas. **27**(11), 1091–1106 (2006)
6. Poza, J., et al.: Extraction of spectral based measures from MEG background oscillations in Alzheimer's disease. Med. Eng. Phys. **29**, 1073–1083 (2007)
7. Abásolo, D., et al.: Entropy analysis of the EEG background activity in Alzheimer's disease patients. Physiol. Meas. **27**(3), 241–253 (2006)
8. Poza, J., et al.: Analysis of neural dynamics in mild cognitive impairment and Alzheimer's disease using the wavelet turbulence. J. Neur. Eng. **11**(2), 026010 (2014)