Biosystems & Biorobotics

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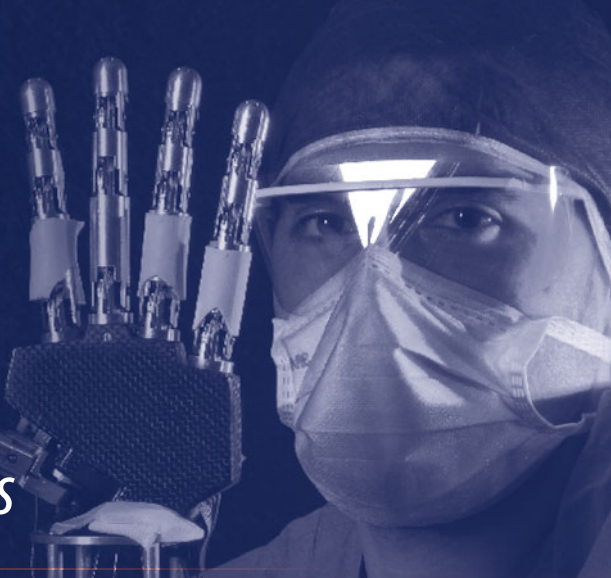

Converging Clinical and Engineering Research on Neurorehabilitation III

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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Contents

Prosthetics – Computer Models in the Design of Neurotechnologies and Rehabilitation Tools (SS3)

Prosthetics – New Perspectives in Upper Limb Prosthetics: from the Robotics Laboratory to Clinical Use (SS4)

Prosthetics – Poster Session

Pre-conference Workshops

Neuroscience – Neural Signal Analysis: Novel Approaches to Understanding Brain Diseases (SS13)

Characterizing Non-stationarity in Alzheimer's Disease and Mild Cognitive Impairment by Means of Kullback-Leibler Divergence

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Abstract. The aim of this study was to characterize the non-stationarity level of resting-state EEG in patients with dementia due to Alzheimer's disease (AD), subjects with mild cognitive impairment (MCI) and healthy controls. A frequency-dependent implementation of the Kullback-Leibler divergence was used to characterize non-stationarity patterns. The results showed a statistically significant increase in non-stationarity for AD patients with respect to controls in the 1–70 Hz frequency range, as well as a less pronounced increase for MCI subjects with respect to controls. These results suggest that EEG activity during short time windows consists of more structured oscillations than that of AD patients or MCI subjects.

1 Introduction

DEMENTIA due to Alzheimer's disease (AD) is a neurodegenerative disease characterized by the accumulation of amyloid-beta and tau proteins [1]. Mild cognitive impairment (MCI) can be seen as an early abnormal state of impairment in cognition and is sometimes considered a prodromal state of AD [2]. Both pathologies are characterized by the alteration of neural activity and information processing in the brain, which is usually more subtle in MCI [3].

This research was supported by 'European Commission' and 'European Regional Development Fund' (FEDER) under project 'Análisis y correlación entre el genoma completo y la actividad cerebral para la ayuda en el diagnóstico de la enfermedad de Alzheimer' ('Cooperation Programme Interreg V-A Spain-Portugal, POCTEP 2014–2020'), by 'Ministerio de Economía y Competitividad' and FEDER under project TEC2014-53196-R, and by 'Consejería de Educación de la Junta de Castilla y León' and FEDER under project VA037U16. P. Núñez and S. Ruiz-Gómez have a predoctoral scholarship from the 'Junta de Castilla y León' and the European Social Fund.

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The aim of the study was to characterize the alterations in electroencephalographic (EEG) activity associated with dementia due to AD and MCI by measuring the level of non-stationarity during the resting-state. Our intention was to find out whether patients with MCI and dementia due to AD will show abnormal levels of non-stationarity in their neural activity. To this end, we used wavelet-based Kullback-Leibler divergence (KLD) as it can quantify the non-stationarity of a signal in the frequency domain [4].

2 Materials and Methods

2.1 Subjects

Sixty subjects took part in the study: 32 AD patients (age 80 [75, 86.5] years, median [interquartile range, IQR]), 10 MCI subjects (age 81.5 [78, 87] years, median [IQR]) and 18 healthy controls (age 76 [73, 82] years, median [IQR]). Patients were diagnosed according to the criteria of the National Institute on Aging and Alzheimer's Association (NIA-AA).

2.2 Electroencephalographic Recordings

EEG signals were recorded by means of a 19-channel EEG System (Nihon Kohden Neurofax JE-921A), according to the International 10–20 system, at a sampling frequency of 500 Hz. Five minutes of resting-state eyes closed EEG activity were recorded. The recordings were then preprocessed in four steps: (i) Hamming window bandpass filtering (0.4–98 Hz); (ii) independent component analysis to remove artifacts; (iii) segmentation into 2 s epochs and (iv) visual rejection of artifacts.

2.3 Continuous Wavelet Transform

Time-frequency analysis can provide additional information that is not apparent in the ongoing EEG, as it is often assumed that changes in EEG power reflect underlying changes in neuronal synchrony [5]. In this study, time-frequency maps were computed using the continuous wavelet transform in the same way as in our previous studies to obtain time-frequency representations (TFR) of each segement of the recordings [6]. The cone of influence was taken into account to avoid edge effects [6].

2.4 Kullback-Leibler Divergence

KLD is a metric that measures the discrepancy between two distributions p_i and q_i [4]. The marginal frequency distribution $tfr(f_i)$ and the temporal TFR distribution $p_{f_i,n\triangle t}$ are described in Eqs. (1) and (2) respectively, while KLD is described in Eq. (3) [4].

$$tfr(f_i) = \frac{1}{N} \sum_{n=1}^{n=N} tfr(f_i \triangle t), \tag{1}$$

$$p_{f_i,n\triangle t} = \frac{1}{N}\frac{tfr(f_i, n \triangle t)}{tfr(f_i)}, \tag{2}$$

$$KLD(f_i) = \sum_{n=1}^{n=N} q_{f_i,n\triangle t} \log_2 \frac{q_{f_i,n\triangle t}}{p_{f_i,n\triangle t}} \tag{3}$$

where $tfr(f_i, n \triangle t)$ is the TFR of the signal at each frequency and time point and N is the number of time points in the TFR. In this study, $tfr(f_i, n \triangle t)$ corresponds with the wavelet scalogram. $q_{f,n\triangle t}$ is the uniform distribution, so that KLD measures how much the TFR differs from it (i.e. how close to being stationary it is). The more stationary the signal is, the closer KLD is to zero [4,6]. In this study KLD was computed between 1 and 70 Hz .

KLD was computed for all two second-length epochs in the 1–70 Hz frequency band. Initially, an exploratory analysis was performed to analyze data distribution. Normality was tested with a Kolmogorov-Smirnov test and homoscedasticity with a Levene test. These analyses revealed that the data did not meet parametric test assumptions. Thus, between-group differences were computed by means of non-parametric tests. A Kruskal-Wallis test was used to detect grand-average statistically significant differences between the three groups and Mann-Whitney U-tests were used to assess the sensor-level between-group differences.

3 Results and Discussion

Figure 1 shows the grand-average KLD values for each group under study. Significant between-group differences were found ($p = 1.89e-6$, Kruskal-Wallis test). AD patients showed the highest level of non-stationarity overall, followed by MCI subjects and finally controls. The sensor-level analysis shown in Fig. 2 also points to clear statistically significant differences between controls and MCI subjects, as well as between controls and AD patients. AD subjects showed widespread higher non-stationarity in their EEG activity than controls, while MCI subjects showed higher KLD than controls in the central region and the left hemisphere.

The statistical differences might suggest that non-stationarity in the EEG activity increases during early dementia. This is further supported by the distribution of grand-average KLD values in MCI, which roughly lie the range of values found in the other two groups, with some subjects closer to the control values and some closer to AD patients. This could mean that the level of non-stationarity is related to whether MCI subjects progress towards AD or not, although another study at a later stage would be needed to support this hypothesis. A possible interpretation of the higher non-stationarity found in AD patients is related to the definition of KLD: it could mean that the EEG activity of controls in the short time windows under study consists of oscillations closer to more stationary, structured rhythms. Moreover, a close inspection of the grand average non-stationarity across the [1 70] Hz spectrum revealed that

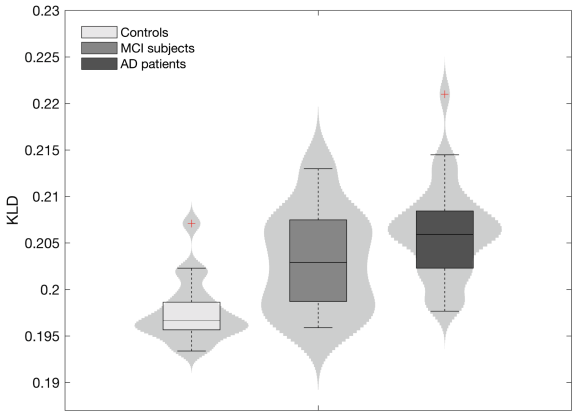

Fig. 1. Violin plots and boxplots depicting normalized grand-average KLD values in the 1–70 Hz frequency band.

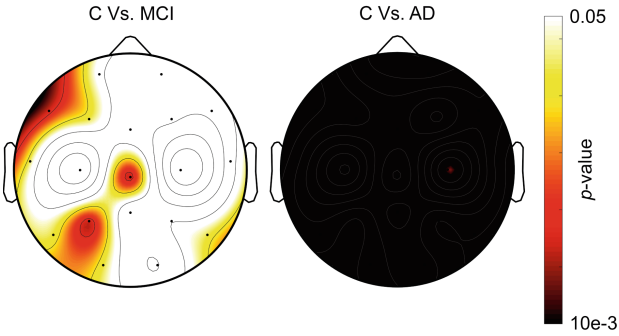

Fig. 2. Topographic maps of the statistical comparisons between controls and MCI subjects, as well as between controls and AD patients (Mann-Whitney U-test with FDR correction).

alpha activity (8–13 Hz) is more stationary for MCI subjects than for controls, suggesting a compensatory mechanism. Finally, in the delta and theta bands (1–8 Hz) EEG activity is more stationary for AD patients than for MCI subjects or controls, hinting at a correlation with the slowing of EEG activity usually found in AD [1,3]. In conclusion, our findings further support the notion that EEG activity in AD and MCI is altered with respect to controls and may be more non-stationary than that of healthy controls in short time intervals.

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