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EEG complexity drug-induced changes in Disorders of Consciousness: a preliminary report.

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***Abstract*— The goal of this work is to investigate EEG (ElectroEncephaloGram) dynamics after drug intake in patients being in states of Disorders Of Consciousness (DOC) after brain injury. Four patients were involved in the study. All the patients exhibit cerebral lesions located in the same anatomical region. Two nonlinear indexes, such as Lempel-Ziv Complexity (LZC) and Approximate Entropy (ApEn), along with power spectra, were calculated for EEG signals gathered from electrodes placed on both injured and non-injured regions. Experimental results show that after drug administration the two nonlinear indexes calculated from EEG taken from injured regions increase ($p < 0.001$) while power spectra decrease or remain unchanged. These results do not pretend to draw conclusions about consciousness level either suggest promising therapeutical treatments, but represent only an experimental evidence about the change in the EEG complexity after drug administration.**

I. INTRODUCTION

Recent clinical improvements in intensive care have increased the number of acute brain injured survivors. Although some of these patients go on to make a good recovery, many of them do not and remain in one of several states now collectively known as Disorders Of Consciousness (DOC). These include the Vegetative State (VS), the Minimally Conscious State (MCS), Severe Disorder of Consciousness (SDC) [1], [2]. The difference between these clinical conditions is the level of awareness that patients show (see Fig. 1). VS is characterized by the complete absence of behavioral evidence for self or environmental awareness, although patients can show spontaneous or stimulus-induced autonomic activity. In this condition, sleep-wake cycles could also be showed [1]. MCS is a condition in which patients show one or more signs of knowledge about self or the environment [2], e.g. they follow simple commands, they recognize verbal or gestural yes/no-responses (accurate or not) or show movements that seem to be beyond mere reflexes. Typically, MCS occurs as a progression from VS, but may also be observed during the course of progressive decline in neurodegenerative diseases. Concerning SDC, it can be globally defined as "severe cognitive disorders" in which the level of cognitive functioning was lost. In spite of recent intensive care advances, the diagnosis and the clinical treatment in DOC patients are still crucial issues.

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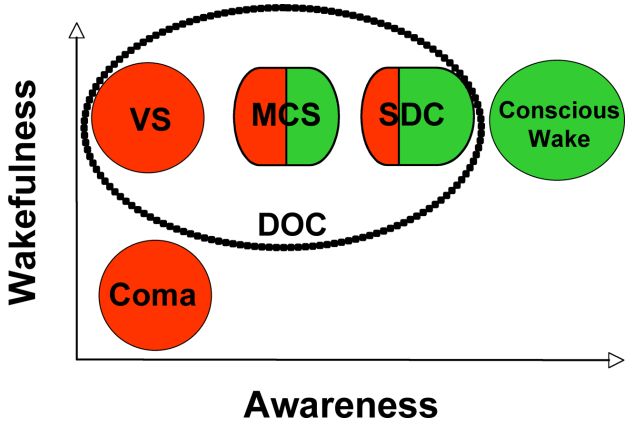

Fig. 1. Conceptual scheme for global disorders of consciousness. Abbreviations: VS, Vegetative State; MCS, Minimally Conscious State, SDC, Severe Disorder of Consciousness and DOC, Disorders Of Consciousness. Green represents the ability to produce voluntary behavior (mobility).

II. CLINICAL DIAGNOSIS AND TREATMENT

The diagnosis of DOC is not easy to make. It has been estimated that at least 40% of vegetative state patients are misdiagnosed [3]. Latest imaging progresses provide a good tool to improve the assessment of disorders of consciousness: although functional neuroimaging can not replace the clinical assessment, it can describe how much the cerebral activity and its regional distribution are different when compared with healthy controls, during rest or after stimuli [4]. Nevertheless, it has been shown that imaging studies are not very reliable: in recent years, despite the great diffusion and success of fMRI, several pitfalls were found [5]. In addition, imaging techniques are too expensive for clinical routine application. Therefore, current clinical practice adopts behavioral criteria, such as neurobehavioral rating scales (Aspen Neurobehavioral Conference Workgroup [1], Royal College of Physicians of London [6]) to detect signs of consciousness [7] in DOC, and Levels of Cognitive Functioning (LCF) Scale [8] to follow the recovery of conscious and communication after trauma in patients with severe cognitive disease. Specifically, Rancho Level of Cognitive Functioning Scale (LCFS) is one of the earliest developed scales used to assess cognitive functioning in post-coma patients [9]. It was developed for planning the treatment, tracking the recovery, and classifying outcome levels. This scale is subdivided into eight levels in which patients can be classified (ranging from "No response" to "Purposeful-appropriate"). Besides the evaluation of cognitive level, another scale, the Glasgow Outcome Scale (GOS), is used to evaluate motor disability

level as well as outcome prediction. This scale attempts to generalize and categorize the outcomes of patients by defining 5 levels (L), from dead (L:1) to Good Recovery (L:5) through the Severely Disabled (L:3). Concerning the clinical treatment, pharmacological intervention is used in DOC clinical practice. Excitatory drugs were proposed in order to overcome the lack of neurotransmitters which leads to a state of unconsciousness and/or unawareness [10]. Against studies that utilize excitatory drugs, in the last few years new pharmacological interventions utilize inhibitory drugs which compete with the inhibitory neurotransmitters since brain injury enhances the neural inhibitory response [11]. Zolpidem is a nonbenzodiazepine sedative in the imidazopiridine class chemically distinct from other sedatives which is used in a normal brain for sleep induction, too. However, in a dormant brain after severe injury, Zolpidem may do the reverse. It increases brain function within 30 min after oral application. This rapid effect distinguishes it from other medicines in DOC such as the dopaminergic medicines that take several weeks to achieve a response [11]. Imaging studies using 99mTc HMPAO Brain SPECT or 18F FDG PET in patients after brain damage have shown that non-functioning areas start functioning again after zolpidem[12].

III. EEG and Disorders of Consciousness

Recent evidences in literature have shown the powerful and reliability of quantitative Electroencephalography (qEEG) in clinical assessment of DOC [13]. The most common EEG pattern in DOC patients could include focal or diffuse continuous slowing of the dominant power spectra in the theta ($4 \div 7.5$ Hz) and/or delta ($0.5 \div 3.5$ Hz) frequency ranges [14]. Loss functional connectivity by coherence analysis is also included [15]. We moved from the assumption that physiological systems have to be considered complex systems as much as any other natural system. Since EEG signals exhibit significant complex behavior [16], a complete characterization could be performed only if its nonlinear and dynamic properties are retained. Accordingly, the usage of higher order statistics and chaotic measures have been proposed [17]. Literature on nonlinear theory reports that many relevant features can be extracted. This work is focused on Entropy and Lempel-Ziv Complexity (LZC). Entropy can be able to discriminate among complex systems, including deterministic, stochastic and composite systems. More in detail, an approximation of Entropy named "Approximated Entropy" (ApEn) can be calculated. It is a statistical parameter that measures the predictability of current values of a physiological signal from its previous values. Many works report on how ApEn measurement can be useful to estimate sleep stages [18] and different brain states. Lempel-Ziv Complexity (LZC) is a useful complexity measure that indicates the rate of appearance of new patterns in a time series. EEG nonlinear indexes might have effect in predicting the prognosis of awakening of both VS and MCS patients. Recently, several papers demonstrated how LZC and ApEn can provide a quantitative measure of the severity of cerebral cortex suppression in VS and MCS. In addition, they are effective in quantifying the response to pain stimulation [19], [20], [21] as well as in predicting outcomes from VS patients. Accordingly, the objective of this work is to comparatively explore drug-induced changes in complexity and power of EEG signals. Based on current literature, two nonlinear indexes, such as Lempel-Ziv Complexity (LZC) and approximate entropy (ApEn), are calculated for signals gathered from electrodes placed on injured and non-injured regions.

IV. Materials and Methods

A. Subjects and Clinical Assessment

The study was performed in the Brain Injury Unit, Department of Neuroscience, Cisanello Hospital, Pisa, Italy. We analyzed four unconscious patients who presented right parietal-temporal lesion. More in detail, two males (being 45 and 69 years old) and two females (24 and 56 years old), one in minimally conscious state (LCFS:3; GOS:3) and three with severe cognitive disorders (LCFS: 5.3 ± 0.5; GOS:3.3 ± 0.5), respectively. The patients were right handed and they had no previous brain injury. The hospital ethical committee approved the study. Informed written consent was obtained from the guardians or relatives of the patients. Brain magnetic resonance imaging (MRIs) scans were obtained from all the patients to ensure the location of brain injuries and exclude obvious communicating or obstructive hydrocephalus.

B. EEG recording

The patients were in non sleeping states during the entire recording process and laid comfortably in a quiet ward. The EEG was recorded using a BrainQuick amplifier System (Micromed, Italy), at positions Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5 and T6, according to the international 10-20 configuration system (electrode impedance $<$ 5 KOhm). A linked earlobe electrode was used as reference. The electrooculogram (EOG) was recorded from two additional electrodes in order to reject off-line the EEG trials corrupted by blinking and eye movement artifacts. To remove the blink artifacts, Independent Component Analysis (ICA) was used. Signals were digitized with sampling rate of 256 Hz, bandwidth 0.1-100 Hz and 12-bit AD conversion resolution. The baseline EEG dataset was recorded before the drug assumption for at least 10 minutes (baseline). After 30 minutes from the drug assumption, another 10 minutes of EEG acquisition was performed in order to study the changes. Since ApEn and LZC were highly sensitive to the presence of high-frequency components in the EEG signal [22] on which, in addition, possible Electromiogram (EMG) artifacts were overlapped,the highest values were considered as outliers and discarded. Signal processing was performed on consecutive intervals of 60 seconds. A sixth-order Infinite Impulse Response (IIR) low-pass filter having cut-off frequency of 30 Hz was used to remove noise over gamma band. The well-known Matlab toolbox EEGLAB [23] was used to process EEG data.

C. Data Selection

Because the injury sites of the patients were quite different, it was rather difficult to evaluate the degree of unconsciousness with full montage. Therefore, in order to compare drug-induced changes in injured and undamaged region, two EEG channels have been chosen for the analysis. According to the MRI scans of all patients, we chose $P4$ and $O1$. The former was used to compare drug-induced changes in injured region and the latter for undamaged region. All features were calculated off-line from pieces of consecutive 60 s intervals for both conditions (pre and post drug assumption).

D. Nonlinear dynamics analysis

1) Lempel-Ziv Complexity (LZC): Before the LZC calculation, we transformed the EEG time series into a simple binary sequence conversion (zeros and ones). By choosing as threshold the mean value of each sequence, data equal or below were converted into the symbol '0', while those above into the symbol '1'. According to the Kaspar and Schuster method [24], the digitalized sequence is scanned in order to compute the complexity index $c(n)$. More specifically, this index counts the number of different patterns in a sequence, starting from short patterns to the longer ones. For instance Lempel-Ziv complexity of $s = 101001010010111110$ is 8, because different patterns observed in s are 1|0|10|01|010|0101|11|110 [24], [25]. To obtain a complexity measure that is independent of the sequence length, $c(n)$ was normalised. For a binary conversion, Lempel and Ziv [26] demonstrated that:

$$\lim_{n \to \infty} c(n) = b(n) \equiv \frac{n}{\log_2 n} \tag{1}$$

such that $c(n)$ could be normalized via $b(n)$:

$$LZC = \frac{c(n)}{b(n)} \tag{2}$$

LZC usually ranges between 0 and 1. LZC can be viewed as independent of number of samples when n is large [25].

2) Approximate entropy (ApEn): *Approximate Entropy* (ApEn) measures the complexity or irregularity of the signal [27], [28]. Large values of ApEn indicate high irregularity and smaller values of ApEn more regular signal. The ApEn was computed as follows. First, a set of length *m* vectors u_j is formed:

$$u_j = (RR_j, RR_{j+1}, ..., RR_{j+m-1}), \tag{3}$$

where $j = 1, 2, ..., N-m+1$, *m* is the embedding dimension, and *N* is the number of measured RR intervals. The distance between these vectors is defined as the maximum absolute difference between the corresponding elements, i.e.:

$$d(u_j, u_k) = \max_{n=0,...,m-1} \{|RR_{j+n} - RR_{k+n}|\} \tag{4}$$

Next, for each u_j the relative number of vectors u_k for which $d(u_j, u_k) \leq r$ is calculated, where r is the tolerance value. The index is denoted with $C_j^m(r)$ and can be written in the form:

$$C_j^m(r) = \frac{\text{nbr of } \{u_k | d(u_j, u_k) \leq r\}}{N - m + 1} \ \forall k \tag{5}$$

Due to the normalization, the value of $C_j^m(r)$ is always smaller or equal to 1. Note that the value is, however, at least $1/(N-m+1)$ since u_j is also included in the count. Then, taking the natural logarithm of each $C_j^m(r)$ and averaging over *j* we obtain:

$$\Phi^m(r) = \frac{1}{N - m + 1} \sum_{j=1}^{N-m+1} \ln C_j^m(r). \tag{6}$$

Finally, the approximate entropy is obtained as:

$$ApEn(m, r, N) = \Phi^m(r) - \Phi^{m+1}(r) \tag{7}$$

Thus, the value of the estimate ApEn depends on three parameters, the length *m* of the vectors u_j, the tolerance *r*, and the data length *N*. In this work we chose $m = 2$. The length *N* of the data also affects ApEn. As *N* increases ApEn approaches its asymptotic value. The tolerance *r* has a strong effect on ApEn and it should be selected as a fraction of the standard deviation of the data (SDNN). A common selection for r is $r = 0.2SDNN$, which is also used in this work.

E. Spectral Analysis

To compare the nonlinear features with traditional qEEG, we also performed spectral analysis, through Fast Fourier Transform, in the typical four bandwidths of the EEG signal, namely δ ($0.5 \div 3.9$ Hz), θ ($4.0 \div 7.9$ Hz), α ($8.0 \div 12.9$ Hz) and β ($13.0 \div 30.0$ Hz).

V. Experimental Results

Analysis was performed by using Matlab (version 2007a). Independent t-tests were used to analyze differences in nonlinear indexes and spectral power between the baseline and drug-intake conditions. Statistical significance was determined as $p < 0.05$. Results in terms of mean and standard deviation are shown in the table I

TABLE I
LZC, ApEn and Power Spectra comparisons among different conditions.

EEG Ch.	Index	Baseline	Post Zolpidem	p
P4	ApEn	0.4978±0.0699	0.6300±0.0173	<0.001*
	LZC	0.2599±0.0307	0.3551±0.0229	<0.001*
	Power δ	29.5148±15.6413	12.1331±1.3168	<0.001*
	Power Θ	16.7758±3.6086	9.3800±1.5112	<0.001*
	Power α	10.5277±1.7292	6.9827±0.7849	<0.001*
	Power β	11.0981±2.4013	11.0220±0.9918	>0.05
O1	ApEn	0.6768±0.0247	0.6893±0.0205	<0.05*
	LZC	0.4064±0.0326	0.4204±0.0260	>0.05
	Power δ	15.6482±3.0470	13.1694±1.6521	<0.001*
	Power Θ	12.0781±1.6453	9.7269±1.0154	<0.001*
	Power α	10.9717±1.9697	8.8817±1.1558	<0.001*
	Power β	15.3339±2.7589	14.1809±1.2901	>0.05

VI. Discussion and Conclusion

This work aimed at characterizing EEG dynamics after drug assumption. Four patients were included in this study, one of them with MCS and three with SDC. All the patients presented right parietal-temporal lesion. After brain injury the inhibitory response dominates [11]. If in a normal brain function Zolpidem enhances excitatory action, in dormant brain may do the reverse and may be able to increase brain functions within 30 minutes after oral application. This rapid effect distinguishes it from other medicines in DOC such as the dopaminergic medicines. Two nonlinear indexes, such as Lempel-Ziv Complexity (LZC) and Approximate Entropy (ApEn), along with power spectra, were calculated for EEG signals gathered from electrodes placed on injured and non-injured regions. Experimental results showed different trends of the two non-linear indexes with respect to power spectra calculated from EEG acquired from injured and non-injured regions, during baseline condition and after administrating drug. More specifically, the two non-linear indexes calculated from EEG from P4 channel in baseline condition are lower than after drug administration condition ($p<0.001$). On the contrary, power spectrum, after the treatment, decreases in δ, θ, α bandwidths with $p < 0.001$ while in β band remains unchanged. The same parameters calculated from EEG acquired from $O1$ region do not undergo a statistically significative change in trend, from baseline to drug-intake condition. As reported in recent literature, techniques derived from non-linear dynamics and chaos theory may be of complementary value in identifying patterns and mechanisms that are not detectable with traditional statistics based on linear models. Our results showed changes in nonlinear index trends, but they do not pretend to give any clinical evidence about possible changes in levels of cognitive functions. Rigorous clinical validations, in terms of metabolic investigation, are necessary to confirm any possible hypothesis. There are some works in literature [19], [20], [21] showing that complexity of EEG increases with the consciousness level. Although these works could easily lead us to conclude that Zolpidem assumption may improve the awareness of patients, we keep away from this conclusion and only show very early results from a preliminary experimental protocol on a few patients. The prospectives go towards the understanding of the underlying physiology of the nonlinear indices as well as the research of other additional reliable parameters.

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References

[1] J. Giacino, S. Ashwal, Childs *et al.*, "The minimally conscious state: definition and diagnostic criteria," *Neurology*, vol. 58, no. 3, 2002.

[2] M. Monti, S. Laureys, and A. Owen, "The vegetative state," *BMJ*, vol. 341, p. c3671, 2010.

[3] C. Schnakers, A. Vanhaudenhuyse, Giacino *et al.*, "Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment," *BMC neurology*, vol. 9, no. 1, p. 35, 2009.

[4] J. Gawryluk, R. D'Arcy, J. Connolly *et al.*, "Improving the clinical assessment of consciousness with advances in electrophysiological and neuroimaging techniques," *BMC neurology*, vol. 10, no. 1, 2010.

[5] D. Jones and M. Cercignani, "Twenty-five pitfalls in the analysis of diffusion MRI data," *NMR in Biomedicine*, vol. 23, no. 7, 2010.

[6] R. C. of Physicians, "The permanent vegetative state: guidance on diagnosis and management. report of a working party." 2003.

[7] S. Majerus, H. Gill-Thwaites, K. Andrews, and S. Laureys, "Behavioral evaluation of consciousness in severe brain damage," *Progress in brain research*, vol. 150, pp. 397–413, 2005.

[8] B. Jennett, J. Snoek, M. Bond *et al.*, "Disability after severe head injury: observations on the use of the Glasgow Outcome Scale." *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 44, no. 4, 1981.

[9] C. Hagen, "The rancho levels of cognitive functioning," *Downey, CA: Rancho Los Amigos Medical Center*, 1998.

[10] Y. Kim, J. Shin, and Y. An, "Effects of methylphenidate on cerebral glucose metabolism in patients with impaired consciousness after acquired brain injury," *Clinical neuropharmacology*, vol. 32, no. 6, p. 335, 2009.

[11] R. Clauss, "Neurotransmitters in coma, vegetative and minimally conscious states, pharmacological interventions," *Medical hypotheses*, vol. 75, no. 3, pp. 287–290, 2010.

[12] C. Brefel-Courbon, P. Payoux, Ory *et al.*, "Clinical and imaging evidence of zolpidem effect in hypoxic encephalopathy," *Annals of neurology*, vol. 62, no. 1, pp. 102–105, 2007.

[13] E. Kobylarz and N. Schiff, "Neurophysiological correlates of persistent vegetative and minimally conscious states," *Neuropsychological rehabilitation*, vol. 15, no. 3, pp. 323–332, 2005.

[14] P. Hansotia, "Persistent vegetative state: review and report of electrodiagnostic studies in eight cases," *Archives of neurology*, vol. 42, no. 11, p. 1048, 1985.

[15] M. Davey, J. Victor, and N. Schiff, "Power spectra and coherence in the EEG of a vegetative patient with severe asymmetric brain damage," *Clinical Neurophysiology*, vol. 111, no. 11, pp. 1949–1954, 2000.

[16] D. Subha, P. Joseph, R. Acharya U *et al.*, "EEG Signal Analysis: A Survey," *Journal of medical systems*, vol. 34, no. 2, 2010.

[17] C. Stam *et al.*, "Nonlinear dynamical analysis of EEG and MEG: review of an emerging field," *Clinical Neurophysiology*, vol. 116, no. 10, pp. 2266–2301, 2005.

[18] N. Burioka, M. Miyata, Cornélissen *et al.*, "Approximate entropy in the electroencephalogram during wake and sleep," *Clinical EEG and neuroscience: official journal of the EEG and Clinical Neuroscience Society (ENCS)*, vol. 36, no. 1, p. 21, 2005.

[19] W. Dongyu, S. Zhiqian, K. Sha *et al.*, "Predicting awakening of unconscious patients with EEG nonlinear analysis," *Chinese Journal of Rehabilitation Medicine*, 2009.

[20] D. Wu, G. Cai, Y. Yuan, Liu *et al.*, "Application of nonlinear dynamics analysis in assessing unconsciousness: A preliminary study," *Clinical Neurophysiology*, 2010.

[21] M. Sarà and F. Pistoia, "Complexity loss in physiological time series of patients in a vegetative state." *Nonlinear dynamics, psychology, and life sciences*, vol. 14, no. 1, p. 1, 2010.

[22] R. Ferenets, T. Lipping, A. Anier *et al.*, "Comparison of entropy and complexity measures for the assessment of depth of sedation," *Biomedical Engineering, IEEE Trans. on*, vol. 53, no. 6, 2006.

[23] A. Delorme and S. Makeig, "EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis," *Journal of neuroscience methods*, vol. 134, no. 1, pp. 9–21, 2004.

[24] F. Kaspar and H. Schuster, "Easily calculable measure for the complexity of spatiotemporal patterns," *Physical Review A*, vol. 36, no. 2, p. 842, 1987.

[25] X. Zhang, R. Roy, and E. Jensen, "EEG complexity as a measure of depth of anesthesia for patients," *Biomedical Engineering, IEEE Transactions on*, vol. 48, no. 12, pp. 1424–1433, 2001.

[26] A. Lempel and J. Ziv, "On the complexity of finite sequences," *Information Theory, IEEE Transactions on*, vol. 22, no. 1, 1976.

[27] Y. Fusheng, H. Bo, and T. Qingyu, "Approximate Entropy and its application in biosignal analysis," *Nonlinear biomedical signal processing*, p. 72, 2000.

[28] J. Richman and J. Moorman, "Physiological time-series analysis using approximate entropy and sample entropy," *American Journal of Physiology- Heart and Circulatory Physiology*, vol. 278, no. 6, p. H2039, 2000.