Non-linear recurrence analysis of NREM human sleep microstructure discloses deterministic oscillation patterns related to sleep stage transitions and sleep maintenance

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Abstract— **Sleep is a dynamic process aimed at obtaining the required neurophysiological states at certain times, according to circadian and homeostatic needs and despite external or internal interfering stimuli. In this context, peculiar transient synchronized EEG patterns (TSEP) are supposed to play the main role in the building up of EEG synchronization and in the flexible adaptation against perturbations Our study aimed at disclosing and quantifying attractor driven, hidden periodicity or, conversely, chaotic oscillation patterns in the series of these TSEP related to sleep stage transitions and sleep maintenance. At first we devised a multistep algorithm, able to capture TSEP from EEG during sleep in 10 healthy volunteers. The time series of TSEP were then analyzed according to the Recurrence Plot (RP). TSEP series showed to form a pseudo-periodic series which becomes progressively denser and more stable until steady slow wave NREM sleep is reached, but looses stability just before REM sleep starts. This suggests that deterministic oscillatory patterns maybe adequate descriptors of the balance between homeostatic needs for NREM sleep and REM sleep pressure, supported by different cortical neuronal populations interactions.**

I. INTRODUCTION

SINCE more than forty years [1] sleep is considered as composed by a macrostructural organization (cyclic alternation of NREM sleep stages and REM sleep) of regular and predictable events.

Actually, this macrostructure of sleep may be considered the result of finer graduations of transient EEG activities (microstructure of sleep). Among these EEG activities, peculiar transient synchronized EEG patterns (TSEP) are supposed to be the expression of EEG synchronizing mechanisms accompanying the dynamic organization and stabilization of NREM sleep, ensuring flexible adaptation against perturbations. TSEP include: a) high voltage, low frequency component of K-complexes; b) transient delta bursts; c) high voltage, low frequency components of the Cycling Alternating Pattern (CAP) described by Terzano et al [2-4]. During normal sleep K-complexes, delta bursts and CAP progressively are grouping in recurring clusters, until steady slow wave sleep (SWS), expression of maximal EEG synchrony and deep sleep, is reached.

Unfortunately, sleep microstructure scoring is difficult and rather time-consuming, due to the variability of event parameters and the complexity of classifications. Automatic detection methods of specific EEG events are therefore very advisable. Up to now some methods based on signal amplitude and typical frequency content [5-6] or on feature-based detection, also using neural networks [7-8] have already been proposed. They are however not very satisfactory because, being based on the detection of fixed amplitude thresholds, they are not very robust with respect to inter- and intra-subject analysis. The method developed and tested by our group [9], on the contrary, is based on an adaptive threshold depending on the intrinsic variability of each EEG recording and TSEP scoring relies on the temporal coincidences between 'candidate TSEP' detected in multiple EEG registration channels. It proved to be able to capture most of the TSEP manually scored by experts. Such automatic tool makes then possible to provide complete time series of TSEP for further analysis.

As normally occurs in biological systems, such series are normally non-stationary, requiring non-linear dynamics techniques, as for instance the use of the Recurrence Plot (RP) and the Recurrence Quantitative Analysis (RQA). The above techniques have already been proposed to analyze EEG signals [10-11] in both the awake and the sleep states, and also in pathological situations, but have never been so far used to evaluate sleep microstructure, i.e. TSEP time series.

II. MATERIAL AND METHODS

A. TSEP detection

Sleep recordings from 10 healthy subjects (5 males, 5 females; mean age 28.5 ± 4.8 years, with normal Body Mass Index (BMI: kg/m2), absence of known sleep disorders and of diseases involving central nervous system or endocrine system; without medication treatment from at least one month before the study) were considered. After an adaptation night, a full-night polysomnography (PSG) in the sleep laboratory was performed, providing measurements of EEG using C3-A2 (Ch1), C4-A1 (Ch2), O1-A2 (Ch3), O2-A1 (Ch4) derivations according the 10-20 international placement system; electrooculogram, electrocardiogram; respiratory effort by thoracic and abdominal strain gauges, air-flow by thermistor, snoring nose by a microphone, arterial oxyhaemoglobin (SaO_2) using a pulse oximeter with

finger probe; submental and tibialis anterior muscles elecromyogram.

The EEG signal sampling rate was 256 Hz ,A/D conversion (10 bit) and filtering were performed (high-pass f=0.6 Hz, low-pass f=15 Hz and notch f=50 Hz).

According to the procedure described in [9], rough data of all EEG signals were exported into a MATLAB program specifically written to detect TSEP by the presence of negative peaks (of amplitude larger than a threshold value, corresponding to 3 time the SD of the recorded signal) preceded by a zero-crossing point ZCP. By sampling the average amplitude of the signal both before and after the ZCP, the 'candidate TSEP' were selected for each EEG channel. Then coincidence between channels were investigated for all possible combinations of channels pairs.

Finally the 'candidate TSEP' were verified by visual inspection and the program provided the values for all onset-onset intervals (inter-TSEP interval) to form the TSEP time series for each sleep. Series were then supervised, excluding stage 1 sleep, which does not present events as described above, while the onset of steady SWS characterized by an uniform pattern of high amplitude slow frequency waves lasting more than 60 s was considered as the terminal point of the previous inter-TSEP series. Similarly, REM periods were not included in the analysis as there is no agreement for the existence of oscillating events during them. As a consequence, for each sleep we obtained a time series whose data were formed by sequences of consecutive inter-TSEP intervals, throughout sleep cycles, with points of discontinuity between sequences when awakenings, stage 1 sleep, steady SWS or REM sleep occurred (Fig. 1) .

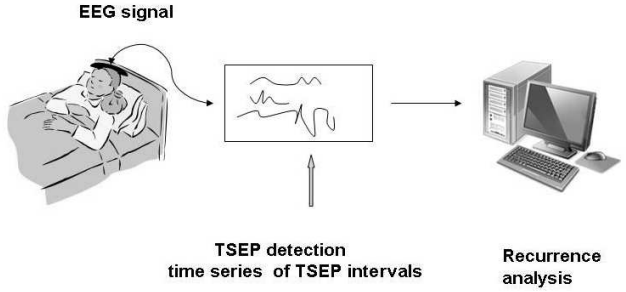

Figure 1. Schematic representation of the experimental procedure: EEG signals were collected from sleep recordings obtained from 10 healthy volunteers, TSEP were detected and the time series of the intervals between two consecutive TSEP were computed. The number of TSEP extracted per sleep (mean ± SD) was 645 ± 124, the inter-TSEP interval duration (mean ± SD) was : 33 ± 28 s, the TSEP duration (mean ± SD) was: 18 ± 15 s. Datasets were then evaluated using the Recurrence Analysis.

B. TSEP analysis

Each time series (TSEP intervals evolving over time), containing approximately 500-700 points, was described as a trajectory in a 2-dimensional phase space with time axes, and visually inspected in order to detect the occurrence of closed loops and basin of attraction. Then the unthresholded Recurrence Plot RP, was produced using the freely-downloadable program *Visual Recurrence Analysis* (VRA) created by E.Kononov [12]. RP were obtained after expanding the series into a higher *m*-dimensional space using the "delayed coordinate embedding" technique (that requires as input parameters: the *delay interval* τ calculated using the "minimal mutual information" technique [13], and the *embedding dimension m,* chosen according to the method of "false nearest neighbours", as described in [14]. Then the phase space was reconstructed

$$x_i = \sum_{j=1}^{m} u_{i+(j-1)\tau}\, e_j \qquad (1)$$

The recurrences of a trajectory $\vec{x}_i \in \mathbb{R}^d$ in phase space were investigated by computing and plotting the distances

$$D_{ij} = \left\| x_i - x_j \right\| \qquad (2)$$

obtaining the so-called unthresholded recurrence plot [15].

A representation of colored dots (i;j), where "hot" colors (yellow, red, and orange) marked recurrence points associated with small distances (i.e. a j-th point p(j) of the trajectory falls into the neighbourhood of a given i-th point p(i)), while "cold" colors (blue, violet) are used to show larger distances was selected. Each point is plotted against itself along the x=y axis so RP is symmetrical along this diagonal. Based on this representation, two characteristics of RPs are analyzed: a) the Typology, that offers a global impression of the large scale evolution of the events and may distinguish between random data series (homogeneous pattern of RP) or oscillating, periodic recurrent events (diagonal oriented pattern of RP); b) the Texture, that refers to the small scale structure of the plot and is able to disclose periodicities or randomness of the time series at the smallest intervals.

III. RESULTS

Fig 2 shows the diagram in the phase-space obtained by plotting a TSEP time series (different colours refer to the 4 different time periods between successive REM phases. The plot evidences that closed loops of different extension occurs for each NREM sleep period, as if attractors towards stable sleep , of different 'strength' were present .

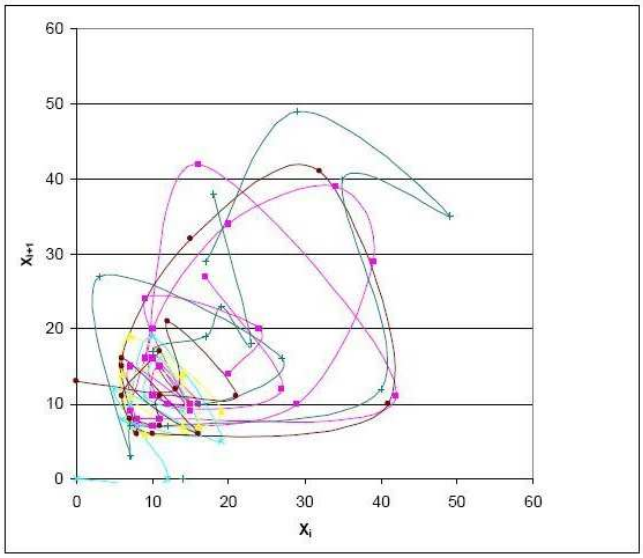

Figure 2. 2D phase-space portrait of a 'reference' sleep (patient AC).

After proper selection of the embedding parameters *m (between 6 and 12) and τ (between 1 and 2)* the unthresholded RPs were obtained (see Fig. 3a). In order to facilitate the interpretation, Fig 3b is reported aswell, representing the hypnograms from the same subject.

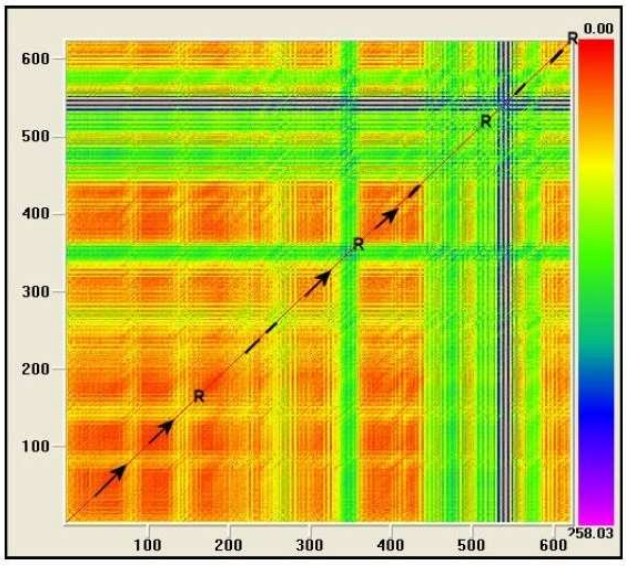

Figure 3a. Recurrence plots obtained by VRA for a reference sleep (patient CA), corresponding to a two dimensional colored representation of recurrences in the original time series of inter-TSEP-intervals. "Hot" colors (yellow, red, and orange) marked recurrence points associated with small distances; "cold" colors (blue, violet) were used to show larger distances. Dots color ranges from red for smallest inter-point distances to violet for largest spacing.
Diagonal black lines in the recurrence plot correspond to TSEP series occurring during stage 3 or 4 sleep, with arrows when the sequence terminates with steady SWS lasting more than 60 s. The portions of diagonal without black line correspond to the TSEP series occurring during stage 2 sleep. The marker "R" corresponds to the occurrence of a REM period between two TSEP series.

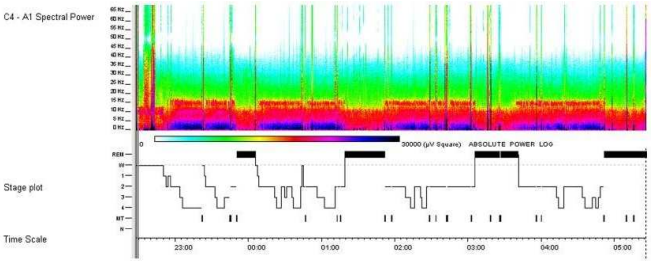

Figure 3b Sleep hypnograms and spectral analysis of the sleep analyzed in Fig. 3a

Three peculiar features are recognizable from the inspection of RP and hypnograms:

I. NREM sleep corresponded to a *Texture* characterized by yellow scattered dots which were progressively replaced by longer diagonals of red dots, in correspondence with unstable SWS (thick black lines in Fig. 3a) or steady SWS (thick black lines terminating with an arrow, in Fig. 3a). Mean inter-TSEP interval preceding steady SWS, considering the first two cycles for all sleeps, was 8.9 ± 7.5 seconds, while higher variability was found in the last sleep cycles (25 ± 28 sec).
II. The descending branches of sleep cycles of in hypnograms (NREM sleep deepening) corresponded to a RP *Typology* characterized by colored blocks of "hot" dots and diagonal oriented patterns, peculiar of periodic and deterministic origin of data, while, on the contrary, the ascending branches of sleep cycles (exit from deep NREM sleep) corresponded to more complex patterns, typical of more random data series.
III. Points in the RP corresponding to REM sleeps (indicated with "R" in Fig. 3a) were always preceded by complex and unstructured RP *Texture* (mixed "hot" and "cold" dots), indicating random data series, random inter-TSEP intervals and no evidence of periodic oscillatory system (lowest level of the oscillatory system to maintain NREM sleep).

IV. CONCLUSIONS

Our study proves that using RP techniques for the analysis of the sleep microstructure is very effective (and provides much more intuitively understandable plots in comparison with traditional 'phase space' trajectories, see Figs 1 and 2a. It also suggests a novel mathematical framework able to disclose, describe and quantify the underlying oscillating neurophysiological synchronizing processes of transient activities during sleep deepening, revealed by EEG. We only describe the behaviour of the dynamical system involved with NREM sleep, and is based on various reasonable hypotheses which can be made about neurological structures and pathways responsible for NREM sleep itself.

In particular, our analysis suggests that "spontaneous"

TSEP may be considered as the cortical expression of an endogenous pre-determined dynamic process, possibly depending from thalamo-cortical loops, that is activated according to the homeostatic needs of NREM sleep, tends to an equilibrium point (attractor) corresponding to steady SWS, and periodically vanishes concomitantly with REM pressure raises. During the construction of EEG synchrony, corresponding to the descending branch of each sleep cycle, TSEP form a deterministic pseudo-periodic series (with an oscillating period (inter-TSEP interval) of about 9 seconds), which becomes progressively shorter and finally stabilizes its recurrence rate (attractor) until steady SWS is reached. After translating this qualitative description in quantitative parameters using RQA, the pseudo-periodical structure of TSEP will be possibly described by a model with two or more interacting cortical and subcortical neuronal populations.

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