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CAP sleep in insomnia : new methodological aspects for sleep microstructure analysis

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Abstract—**This work aims to propose new methodologies for the quantitative characterization of insomnia. Sleep microstructure, as expressed by Cyclic Alternatic pattern (CAP) sleep, is studied and differences between normal sleepers and insomniacs are investigated. The dynamic in the structure of CAP activation events is studied by use of wavelet analysis and the content of events, i.e. EEG dynamics, is studied in terms of complexity analysis. Both in structure and content, features exhibiting statistically significant differences are proposed, opening new perspectives for the understanding and the quantitative characterization of sleep and its disorders.**

I. Introduction

INSOMNIA is a prevalent condition in Western countries, and a common complaint in general practice and psychological counseling. It has been related to the rising societal or economic demands of our 24/7 societies [1].

In the major diagnostic systems, such as the Diagnostic and Statistical Manual, 4th edition (DSM-IV), insomnia is considered as a sleep disorder when difficulty with the initiation, duration, maintenance, or quality of sleep occurs repeatedly (i.e. at least one month), despite adequate time and opportunity for sleep and results in some form of daytime impairment on an emotional, social or professional level. When such diagnostic criteria are applied, the estimated prevalence of insomnia is about 10 % [2]. Finally, in terms of insomnia's «cause», it is frequently classified as primary or secondary due to another condition.

In current practice, in the evaluation of insomnia the measurement of subjective and objective sleep parameters such as total sleep time, number and duration of awakenings, sleep onset latency and sleep quality are the most important features assessed [3]. Polysomnography-based quantitative sleep indices and subjective reports of disturbed sleep do not always exhibit a clear relation, which leads to a grey zone in insomnia diagnosis and treatment.

The need for the establishment of quantitative criteria of insomnia is evident, and in the last years, effort was paid to extend the investigation of sleep mechanisms in normal and pathologic sleep. Analysis of sleep microstructure mechanisms, EEG arousals and CAP sleep, has been proven as an interesting direction for sleep disorders investigation.

CAP sleep is manifested as phasic arousals during non-rapid eye movement (NREM) sleep, consisting of repetitive spontaneous sequences of transient events (phase A of subtypes A1, A2 and A3) with intervals of intermittent recovery (phase B) that separate the repetitive elements, having a cyclic nature following the multisecond oscillation [4]. CAP sleep has been regarded as a mechanism essential in creating sleep macrostructure, i.e. CAP modulates the onset, consolidation and disruption of all sleep stages [5]. Based on this interpretation of CAP, it is a reasonable and worth-examining hypothesis to consider differences in CAP mechanisms as the background for unstable sleep and related sleep disorder manifestations.

The aforementioned hypothesis concerning CAP sleep has been examined in the case of primary insomnia, and the main findings include a significant increase of CAP rate, subtypes A1 and A2, EEG arousals (subtype A3), nocturnal wakefulness and stage 1, and reduced values of total sleep time and slow wave sleep in insomniacs, as compared to controls [6]. These findings suggest that the sleep of insomniacs contains more sleep instability as measured by CAP parameters.

In the present work, a further step is taken as regards the potential differences in CAP sleep between normal and insomniac subjects. Moving beyond the comparison of the overall time in CAP sleep in NREM (CAP Rate) and the number of events that build up the CAP sleep (A1, A2 A3 activation subtypes), the aim of the proposed methodologies is twofold:

a) to examine differences in the structure, i.e. dynamics in occurrence of CAP events , and

b) to examine differences in the content, i.e. morphology of EEG within these events.

The innovation of the proposed approaches lies both in the methodologies followed, resulting in new features describing CAP sleep, and in the consolidation of quantitative criteria that highlight the deviations in sleep mechanisms present in

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insomniac patients and can successfully discriminate normal sleep from insomnia.

II. METHODS

A. Polysomnographic Data and Annotations

The study was carried out on 11 healthy adult subjects, 5 male and 6 female, aged between 25 and 45 years (mean 32.7yrs), with no sleep complaints, comprising group N, and 10 subjects diagnosed with primary insomnia, 4 males and 6 females, mean age 32.5 yrs (group I). The sleep polysomnographic recordings (PSG), one per subject, were provided by the Parma University Sleep Disorders Center. Sleep analysis was carried out after adaptation night to the sleep lab for screening purposes and adjustment.

1) *Sleep structure annotation description*. Hypnogram and CAP scoring were performed by sleep experts, following standard approaches. The macrostructure was defined according to conventional R&K rules, leading to a characterization of sleep stage every 30 s, while CAP scoring was based on published guidelines [4], resulting in a characterization of CAP segments and the activation subtypes with 1 sec resolution. Therefore, the sleep structure information (sleep stage, CAP, activation type) was eventually available on a sec by sec, enabling the transformation of this information to a timeseries for further processing.

2) *EEG data preprocessing*. A single unipolar EEG derivation per subject was used for this analysis, either C3-A2 or C4-A1. The signal was sampled at 100 Hz, and bandpass-filtered at 0.3-40 Hz.

B. The CAP sleep structure and features

Wavelet analysis of CAP structure is proposed, following the steps described below:

1) Encode the CAP annotation timeseries as A1 -> 1, B1 -> -1, and 0 otherwise, for parts that are within CAP segments, and thus make a time series T_{AB} of consecutive {1, -1, 0} values. Here, the focus is on A1 activation subtype, but other or all subtypes could be similarly encoded.
2) Apply the discrete wavelet transform in the T_{AB} timeseries, with Daubechies mother wavelet (DB11), in 12 scales.
3) Calculate the energy percentage and wavelet entropy per band, as described below, to be later used features for comparison between groups N and I.

WE(s_i), i.e. normalized wavelet energy, as in (1), calculates the percentage of energy corresponding to each scale s_i.

$$WE(s_i) = 100 \frac{\sum_{j=1}^{L_i} w^2(s_i, j)}{\sum_{s_i} \sum_{j=1}^{L_i} w^2(s_i, j)} \quad (1)$$

where s_i is the scale, s_i =1, 2, …12. L_i is the total number of wavelet coefficients in scale s_i, and $w(s_i,j)$ is the j^{th} wavelet coefficient in scale s_i.

Wavelet Entropy *WEn(s_i)*, as in (2), applies the Shannon entropy, with the convention 0log0=0, using as input the positive wavelet coefficients w_p , instead of a probability density function.

$$WEn(s_i) = -\sum_{j=1}^{L_i} w_p^2(s_i, j) \log(w_p^2(s_i, j)) \quad (2)$$

Wavelet entropy can signify the complexity of a non-stationary signal or system in both time and frequency domain [7]. The correspondence between scales and time period zones of the expressed phenomena is depicted in Table I. It can be seen that the 12 scales can express phenomena spanning from seconds to hours.

TABLE I
THE TIME PERIODS OF PHENOMENA, AS INVERSE OF THE FREQUENCY BAND, PER WAVELET SCALE, STARTING FROM SAMPLING FREQUENCY 1HZ, AND THEREFORE SPECTRUM <= 0.5HZ, I.E. PERIOD 2 SEC.

	Sec		Minute		Hour	
Scale	min	Max	Min	Max	Min	max
s_1	2	4	0.03	0.07	0.0006	0.0011
s_2	4	8	0.07	0.13	0.0011	0.0022
s_3	8	16	0.13	0.27	0.0022	0.0044
s_4	16	32	0.27	0.53	0.0044	0.0089
s_5	32	64	0.53	1.07	0.0089	0.0178
s_6	64	128	1.07	2.13	0.0178	0.0356
s_7	128	256	2.13	4.27	0.0356	0.0711
s_8	256	512	4.27	8.53	0.0711	0.1422
s_9	512	1024	8.53	17.07	0.1422	0.2844
s_{10}	1024	2048	17.07	34.13	0.2844	0.5689
s_{11}	2048	4096	34.13	68.27	0.5689	1.1378
s_{12}	4096	8192	68.27	136.53	1.1378	2.2756

C. The CAP sleep content

Sample Entropy (SampEn)is employed for the assessment of potential differences in the content of sleep events, i.e. in EEG morphology within the event. SampEn is considered as a measure of the regularity of a time series, being thus informative about the underlying complexities in the processes giving rise to it. In a previous work [8], EEG SampEn was employed to characterize the different sleep macrostructure and microstructure events. Here, the SampEn has been calculated in consecutive 5 s windows, without overlap, with parameters m=2 and r=0.25. A SampEn timeseries, *SE(t)*, is eventually constructed with values on a per second basis, by attributing the SampEn value calculated in the 5s window to all the five seconds in the window.

As overall features, characterizing the morphology of biphasic events in CAP sleep, the following features are considered:

1) $mSEA1_{st_i}$ and $mSEB1_{st_i}$ as the mean value of *SE* in sleep stage st_i and in CAP sleep, during activation phase of subtype A1 and deactivation phase B1, respectively.
2) $mSEBa_{st_i}$ as the mean of *SE* in background activity (nonCAP) in sleep stage st_i.

The following ratios, as in (3) and (4), are considered for comparison between groups N and I:

$$nABB\,(st_i) = \frac{mSEA\,1_{st_i} - mSEB\,1_{st_i}}{mSEBa_{st_i}} \quad (3)$$

$$AB\,(st_i) = \frac{mSEA\,1_{st_i}}{mSEB\,1_{st_i}} \quad (4)$$

Feature nABB(st_i) expresses the effect in EEG complexity taking place during the phasic event of A1 activation and the following deactivation, (i.e. A1 – B1 oscillation), normalized to the complexity of background activity. Feature AB(st_i) expresses the activation complexity to deactivation complexity ratio.

D. Statistical Analysis

The calculated features are tested for statistically significant differences between the two groups, N and I. The pool of available features for statistical analysis includes 24 (12 scales x 2) features for structure and 6 (2x3stages) features for content.

TABLE II
OVERALL SLEEP STRUCTURE CHARACTERISTICS OF THE SLEEP DATA UNDER EXAMINATION.

	Insomnia (10 subjects)	Normal (11 subjects)
Total number of samples	303255	320170
Mean PSG time	8.42	7.65
Mean CAP/NREM ratio*	0.69	0.43
A1 mean time	0.69hrs	0.61hrs
A2 mean time	0.16hrs	0.22hrs
A3 mean time**	0.28hrs	0.15 hrs

*p< 0.0001, **p=0.0062

III. RESULTS

As a basis for further analysis, the CAP sleep time statistics are reported in Table II. Overall, it can be seen that CAP/NREM ratio (CAP Rate) is higher in insomnia, in agreement with what is already reported in [6]. This difference is statistically significant in our dataset, with p< 0.0001 between normal and insomniac sleep.

TABLE III
STATISTICALLY SIGNIFICANT DIFFERENCES IN A1 WAVELET-BASED STRUCTURE FEATURES

	Normal	Insomnia	p
$WE(s_1)$	4.23±0.92	5.07±0.34	0.014839
$WE(s_2)$	5.49±1.54	6.53±0.45	0.053693
$WE(s_3)$	12.77±5.03	17.28±1.14	0.014403
$WE(s_7)$	6.10±1.32	4.70±0.98	0.012426
$WEn(s_1)$	117.38±29.12	222.76±59.86	0.000236
$WEn(s_2)$	106.13±46.67	159.26±32.12	0.006796
$WEn(s_3)$	-208.57±207.94	-692.50±237.72	0.000104
$WEn(s_4)$	-1049.68 ±607.83	-1875.97 ±771.99	0.014898
$WEn(s_{10})$	-72.62±55.63	-147.75±74.91	0.019419

A. CAP Structure

Moving beyond the overall time statistics, the structure of events is examined (see Table III), following the method described in II.B.

Wavelet features with statistically significant differences between the two classes are found in scales s_1-s_4 (<=30 s), s_7 (2-4.5 min, i.e. in the range of a sleep stage) and s_{10} (0.5-1 hr, i.e. in the range of a sleep cycle). Most discriminant features are found in scales 1-4, i.e. in phenomena with scales up to 1min.

It can be seen in Fig 1, that in these small scales, wavelet energy percentage is higher in group I, while in higher scales, the opposite occurs, i.e. wavelet energy in group N is higher for scale s_5 and above corresponding to phenomena spanning in the range of a minute. This can be related with greater variation in the small scales for insomniacs, i.e. high A1-B1 fragmentation within CAP.

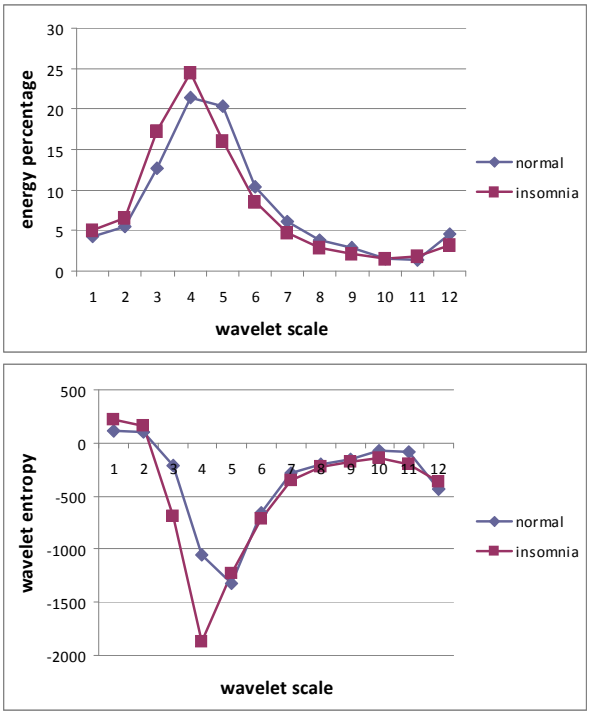

Fig. 1. Average value of *WE* per wavelet scale (top), and *WEn* per scale (bottom), for the groups N and I (normal sleep and insomnia, respectively).

With respect to WEn, positive values imply the presence of many wavelet coefficients with values 0 < c < 1 (log negative), while prevalence of wavelet coefficients with values >1 leads to negative entropy values. Most entries in Table 4 have negative values, with insomnia entropy higher than normal entropy, potentially revealing the spreading of A/B events.

B. CAP sleep and EEG Complexity

Furthermore, the difference in EEG complexity between A1 and B1 segments was assessed via the features *nABB* and *AB*. The difference in complexity of the A1 activations and B1 deactivations, where complexity is expressed by SampEn, is depicted in fig 2, for sleep stage 2. It can be seen that B1 differs in the two groups more than A1.

The mean values and ranges, along with the statistically significant differences between groups N and I are depicted in Table IV. Both features *nABB*(st_i) and *AB*(st_i) have significant differences between the two groups in sleep

stages 2, 3 and 4 (st_2, st_3 and st_4, respectively), except for *nABB*(st_3). The *nABB* measure shows bigger difference between A1 and B1 in group I than in group N. Similarly, the A1 to B1 ratio (*AB*) has smaller values, i.e. A1 smaller than B1, in group I as compared to group N.

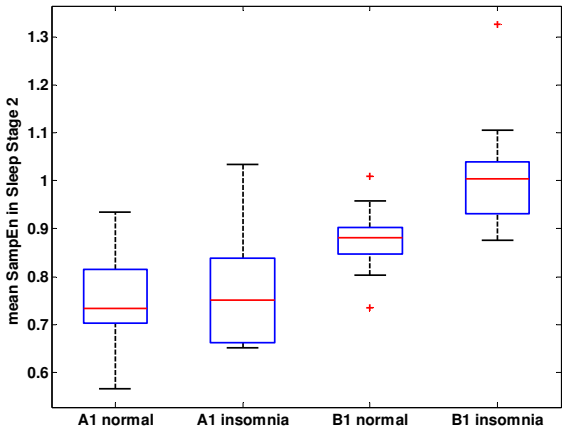

Fig. 2. Distribution of the mean SampEn in A1 and B1 in sleep stage 2, for groups N and I.

It seems that for insomniacs there is difference in the activation-deactivation "oscillation", or rather a more imbalanced oscillation, with a bigger rebound effect in B1 phase, as compared to normal group.

TABLE IV
OVERALL SLEEP STRUCTURE CHARACTERISTICS OF THE SLEEP DATA UNDER EXAMINATION.

	Insomnia	Normal	P value
nABB(st_2)	-0.23 ±0.038	-0.13 ±0.106	0.0101
nABB(st_3)	-0.22 ±0.021	-0.15 ±0.1	0.0528
nABB(st_4)	-0.23 ±0.038	-0. 094 ±0.13	0.0052
AB(st_2)	0.75 ±0.03	0.85 ±0.11	0.0146
AB(st_3)	0.76 ±0.019	0.83 ±0.11	0.0393
AB(st_4)	0.78 ±0.035	0.92 ±0.12	0.0032

It has to be noted that this difference in SampEn is not observed as regards activation subtype A3, where statistically significant differences are observed for *NABB* and for *AB* only in sleep stage 2.

IV. DISCUSSION

In this work, new CAP-related features are proposed, referring to the structure and morphology of CAP sleep, which present statistically significant differences between normal sleep and insomnia.

With respect to the structure of A1 and B1 phases, wavelet energy in the 12 scales of discrete wavelet transform for the biphasic A1-B1 events show that in insomnia, there is higher energy percentage in small scales, and therefore shorter phases and faster changes between the two phases. On the contrary, in normal subjects energy percentage is higher in bigger scales, corresponding to CAP phenomena of longer periods. Additionally, wavelet entropy, as a measure of the complexity of a non-stationary signal, highlights the significantly higher complexity in short scales in insomnia, which could be related to the higher fragmentation of CAP sleep events, and the inability to efficiently build macrostructure.

With respect to CAP sleep content, SampEn as a measure of EEG complexity is employed, and the characteristics of activation-deactivation oscillation in A1 subtype of CAP activation are studied. A phenomenon of higher B1 deactivation is found to be related to insomnia.

The initial results of these innovative methodologies are promising, and suggest new possibilities in the investigation of insomnia, and sleep disorders, potentially serving in the distinction among different aetiologies of poor sleep. In order to further unfold this potential, wider investigation is needed including the employment of different encodings of the CAP subtype (A1-A2-A3) events, independently or combined, further study of EEG complexity measures, and the association between structure and content characteristics. Although the use of a single electrode has practical advantages, the investigation of spatial information could further enrich the proposed methodology. Finally, a more extensive validation of these concepts and the classification performance of the proposed scheme are required.

V. CONCLUSIONS

This work is a first step towards establishing detailed quantitative criteria for insomnia, based on CAP sleep.

With respect to of insomnia and other sleep disorders, PSG investigation extended to CAP variables and EEG arousals can have a significant impact for the diagnosis of primary insomnia, evaluation of treatment efficacy in quantitative terms, and eventually, establishment of unobtrusive methods for disease monitoring and management.

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