35th Annual International Conference of the IEEE EMBS
Osaka, Japan, 3 - 7 July, 2013

Insomnia types and sleep microstructure dynamics

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Abstract— **This work aims to investigate *s*leep microstructure as expressed by Cyclic Alternating Pattern (CAP), and its possible alterations in pathological sleep. Three groups, of 10 subjects each, are considered: a) normal sleep, b) psychophysiological insomnia, and c) sleep misperception. One night sleep PSG and sleep macro- micro structure annotations were available per subject. The statistical properties and the dynamics of CAP events are in focus. Multiscale and non-linear methods are presented for the analysis of the microstructure event time series, applied for each type of CAP events, and their combination. The results suggest that a) both types of insomnia present CAP differences from normal sleep related to hyperarousal, b) sleep misperception presents more extensive differences from normal, potentially reflecting multiple sleep mechanisms, c) there are differences between the two types of insomnia as regard to the intertwining of events of different subtypes.**

The analysis constitutes a contribution towards new markers for the quantitative characterization of insomnia, and its subtypes.

I. Introduction

Insomnia is considered as a sleep disorder characterized by a) repeated difficulty with the initiation, duration, maintenance, or quality of sleep (at least for one month), despite adequate time and opportunity for sleep and b) some form of daytime impairment on an emotional, social or professional level, according to the Diagnostic and Statistical Manual, 4th edition (DSM-IV). Insomnia is common and often persistent [1], being also a major cause for reduced wellbeing, leading to a high societal impact [2]. Two types of insomnia are considered here, Psychophysiological Insomnia (PsI) and Paradoxical Insomnia/Sleep Misperception (Mis), and are compared to normal sleep (Nor). Both types present subjective complaints of poor sleep, and involve stress, but have a different sleep quantity and structure. PsI is a disorder of learned sleep-preventing associations, while Mis does not present objective evidence of sleep quantity disturbance.

Recently, these disorders have been studied with promising results in terms of the detailed structure (microstructure) of sleep activations, and specifically with respect to Cyclic Alternating Patterns of sleep (CAP). CAP sleep occurs during NREM sleep, as repetitive spontaneous sequences of transient events or activations (phase A of subtypes A1, A2 and A3) with intervals of intermittent recovery or deactivations (phase B) that separate the repetitive elements, and this biphasic oscillation has a cyclic nature. Regarding the three A phase subtypes, each phase A subtype has different characteristics, and role: subtypes A1 promote EEG synchronisation, accompanying the transition from light to deep sleep, while, subtypes A2 and A3 are expressed with more desynchronised EEG patterns towards the onset of REM sleep. CAP sleep has been regarded as an essential mechanism in modulating onset, consolidation and disruption of sleep stages [3], and thus its detailed study may shed light in the mechanisms of insomnia.

Regarding primary insomnia (which may include both PsI and Mis), patients under placebo showed a significant increase of CAP rate, subtypes A1 and A2, EEG arousals, nocturnal wakefulness and stage 1, associated with reduced values of total sleep time and slow wave sleep (stages 3 and 4) [4]. In [5], Mis and Nor groups were compared, in terms of sleep staging, and CAP parameters. Patients and controls presented non-significant differences in the amounts of objective sleep time and objective sleep latency, while total CAP rate were significantly higher in misperceptors, and particularly CAP rate in sleep stages 1 and 2. In [6], the CAP rate reduction and deep sleep increase was reported for PsI patients with a hypnotic medication. In a recent work [7], primary insomnia patients were compared with normal in terms not only of CAP rate, but also as regards rates and dynamics of CAP subtypes (B1 and A3 rates, dynamics of A1/B1, and A3/B3).

In the present work, a further step is taken as regards the potential differences in CAP sleep between normal and insomniac subjects, considering separately PsI, Mis and Nor groups. Besides the differences in the amount of CAP, the dynamics of the different types of events, i.e. A1-2-3 subtypes, which correspond to different function, and the way that they are intertwined, are studied. Differences between normals and insomniancs, or between Mis and PsI are investigated.

II. Methods

A. Data Description

The study was carried out on three groups, the normal sleepers (group Nor), the psychophysiological insomnia group (group PsI) and the misperception group (group Mis). Group Nor consisted of 10 healthy adult subjects, 3 male and 7 female, mean age 36 yrs, with no sleep complaints. Group PsI included 10 subjects diagnosed with psychophysiological insomnia, 4 males and 6 females, mean age 41.5 yrs. Group

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Mis consisted of 10 subjects with paradoxical insomnia (also known as sleep state misperception), 4 males and 6 females, mean age 36.2 yrs. One sleep PSG recording per subject was provided by the Parma University Sleep Disorders Center. Sleep analysis was carried out after adaptation night to the sleep lab for screening and adjustment.

B. Sleep structure and CAP Sleep features

Basic features reflecting total times of sleep macrostructure are calculated, as a reference for the groups in focus. Specifically, the total time Awake, total time in NREM, Deep Sleep (s), S4, S2 are calculated.

Additionally, total times and rates of sleep microstructure, in terms of CAP, are calculated, as total time in CAP, CAPrate (CAPtime / NREM time), and rates of each subtype (A1-2-3 , B1-2-3 in NREM) as well as rates of each subtype per sleep stage (e.g. A3/S2 means total time of A3 subtype found in sleep stage 2).

C. Microstructure Event Encodings

Moving beyond the total times and rates, in order to analyse the dynamics of activations, the series of these events have to be numerically encoded. Different encodings are proposed here, emphasizing on either a specific type of activation, or their combination, denoted as TAB (which stands for timeseries of A and B events). TAB_j timeseries with length N (seconds), with each sample $TAB_j(k)$ representing the microstructure information in second , represents the alternation between CAPtime samples (seconds) annotated as subtype activation Aj and deactivation Bj, or none, where. j can take values 1, 2 or 3 (activation subtypes). By selecting to encode exclusively events Aj (1) or Bj (-1), focus is given on one CAP subtype of activation – deactivation. The resulting time series TAB_j consists of consecutive {1, -1, 0} numbers.

$$TAB_j(k)=\begin{cases}1,\ k\in SA_j\\ -1,\ k\in SB_j\\ 0,\text{otherwise}\end{cases},\ \mathrm{j}=1,2,3\ k=1..N \tag{1}$$

where SA_j and SB_j are the sets of Aj or Bj event points. In TAB_A, all three types are taken into account and values j=±1,2,3 are then assigned to the respective activation/deactivation subtypes Aj/Bj. This encoding focuses on the combination and interaction of all activation subtypes.

$$TAB_A(k)=\begin{cases}j,\ k\in SA_j\\ -j,\ k\in SB_j\\ 0,\text{otherwise}\end{cases},\ \mathrm{j}=1,2,3\ k=1..\mathrm{N} \tag{2}$$

D. Short and long-term variation of Activation Timeseries

The short-term and long-term variability, denoted as $SD1$ and $SD2$, of a timeseries X can be estimated as in (3):

$$\begin{aligned}&x^+=(x_1,x_{2.},\ldots,x_{N-m})\\ &x^-=(x_{1+m},x_{2+m.},\ldots,x_N)\\ &x_1=\frac{x^+-x^-}{\sqrt{2}},x_2=\frac{x^++x^-}{\sqrt{2}}\\ &SD1=\sqrt{Var(x_1)},SD2=\sqrt{Var(x_2)}\end{aligned} \tag{3}$$

These have been used in HRV, and provide quantitative indices related to the Poincare plot ellipse [8]. Here m=30s, i.e. larger than the mean duration of an activation. The short and long-term variation can be calculated on all types of encoded activations timeseries.

E. Wavelet Complexity of Activation Timeseries

Wavelet energy and complexity are calculated via discrete wavelet transform with *'db11'* mother wavelet in 12 scales. Considering a sampling frequency fs=1Hz, these scales correspond to time periods from s_1=2-4s, s_2=4s-8s, s_3=8s-16s, s_4=16s-32s, s_5=32s-64s, s_6=1.-2min, s_7=2.-4min,.., s_{12}=68-136min. In each wavelet scale s_i, $i=1,2,\ldots,12$, energy and entropy features are calculated, as described below. More details can be found in [7].

If s_i is the scale, for i=1..12, L_i is the total number of wavelet coefficients in scale s_i, and $w(s_i,k)$ is the k^{th} wavelet coefficient in scale s_i.

Normalized wavelet energy $WE(s_i)$, as in (4), calculates the percentage of energy for each scale s_i.

$$WE(s_i)=100\frac{\sum_{k=1}^{L_i}w^2(s_i,k)}{\sum_{s_i}\sum_{k=1}^{L_i}w^2(s_i,k)} \tag{4}$$

Wavelet Entropy $WEn(s_i)$ applies the Shannon entropy, using as input the normalized wavelet coefficients w_n , in the place of a probability density function, according to (5):

$$WEn(s_i)=-\sum_{k=1}^{L_i}w_n^2(s_i,k)\log(w_n^2(s_i,k)) \tag{5}$$

where $w_n(s_i,k)$ is the absolute value of the wavelet coefficient $w_j(s_i,k)$ normalized to the total energy of all the wavelet coefficients. Alternatively, when a local energy normalization per scale is employed before entropy calculation, the *locally normalized Wavelet Entropy* $nWEn_j(s_i)$ is calculated with a formula analogous to (5).

F. Wavelet Cross-Spectrum and Coherence

Cross wavelet analysis (XWT) and wavelet coherence are powerful methods for testing possible linkages between two time series. The wavelet coherence can be regarded as a localized correlation coefficient in time frequency space [9]. Here a possible locking or linkage between the TAB_1 and TAB_3 timeseries (A1/B1 and A3/B3 phenomena) are in focus. The cross wavelet transform (XW_{XY}) of two time series X and Y is defined as in (6)

$$XW_{XY}=W_X\cdot W_Y^* \tag{6}$$

where Wx and W_Y are the wavelet transforms of X and Y (here TAB_3 and TAB_1), and * denotes complex conjugation.

The wavelet coherence WC_{XY} calculated from the cross-wavelet W_{xy} by normalizing to the magnitude of both W_X and W_Y, as in (7)

$$WC_{XY}=\frac{|S(W_{XY})|^2}{|S(W_X)|^2\cdot|S(W_Y)|^2} \tag{7}$$

where S is a time-scale smoothing operation. Continuous Wavelet transform was calculated here with mother wavelet

'*cgau3',* and scales 4-256, which can describe phenomena from 30 sec to 20 min. Three features: mean magnitude and mean phase of crosswavelet (XWm_{13} and XWp_{13}) and mean magnitude of coherence (WCm_{13}) are considered for comparisons.

G. Statistical Analysis

Kruskal-Wallis non-parametric test is used to show differences among the three groups, testing the hypothesis that they are not the same. Post-hoc analysis with Bonferroni correction shows the different groups. In the CAP dynamics, we choose to show only those features that also stand against an ANOVA comparison with CAPtime as second factor, i.e. those that convey information beyond CAPtime. Finally, the differences between Mis and PsI are statistically analysed by non-parametric analysis and ranked.

TABLE I. MACROSCOPIC FEATURES AND KRUSKAL-WALLIS STATISTICS. I, N AND M REFER TO PSI, NOR AND MIS MEDIAN VALUES

Feature	p-values, median and 27-75% quartiles			
	P	***Nor***	***PsI***	***Mis***
Awake (min)	0.0100 I>N,M	28.5 [19.5 67]	86.96 [45.5 117]	39.25 [22.5 48.5]
NREM (min)	0.0138 I < M	327.7 [286.4 377.5]	308 [294 325]	344 [331 357]
CAP (min)	0.0042 M>N	105.3 [96.9 128.9]	142.6 [112.4 164.0]	184.7 [146.8 223.7]
CAPrate	0.0025 M>N	0.354 [0.282 0.426]	0.496 [0.380 0.537]	0.521 [0.435 0.669]
Deep Sl (min)	0.0108 I<N	137.25 [98.5 151.5]	83.25 [63 91.5]	97,75 [87 112.5]
S4 (min)	0.0144 I<N	87 [57 90.5]	47.75 [29.5 65]	66.25 [47 72]
S2 [min]	0.0254 M>N	186 [156.5 200.5]	201.25 [155.5 227]	233.25 [213.5 240.5]
A3 / NREM	0.0017 M,I>N	0.0254 [0.012 0.035]	0.045 [0.038 0.053]	0.059 [0.047 0.078]
B3 / NREM	5e-004 M,I>N	0.0462 [0.033 0.066]	0.105 [0.078 0.130]	0.109 [0.086 0.151]
A3 /S1	0.0276 M>N	0.060 [0.007 0.081]	0.113 [0.070 0.175]	0.132 [0.071 0.192]
B3 / S1	0.0420	0.107 [0.014 0.184]	0.203 [0.157 0.309]	0.259 [0.101 0.334]
A3 / S2	0.0018 M>N	0.028 [0.016 0.044]	0.053 [0.043 0.072]	0.076 [0.059 0.091]
B3/S2	0.0010 M,I>N	0.065 [0.055 0.106]	0.119 [0.104 0.146]	0.148 [0.134 0.180]
A1 / S4	0.0229 M>N	0.0575 [0.025 0.084]	0.100 [0.071 0.146]	0.14 [0.09 0.19]
B1 /S4	0.0142 M>N	0.182 [0.086 0.383]	0.40 [0.25 0.52]	0.48 [0.41 0.51]
A3 / S4	0.0097 M>N	0.0015 [0 0.0047]	0.0048 [0 0.012]	0.0102 [0.0063 0.0142]

III. RESULTS

Regarding the differences in sleep macrostructure features, as depicted in Table I, it can be observed that Mis and PsI present some different patterns: lack of deep sleep in Psy, and abundance of light sleep in Mis. CAPtime and rate are increased as expected. Furthermore, there are subtype specific differences compared to Nor, mostly concerning increase of A3 and B3, and especially B3 in stage 2, in both PsI and Mis, which may reflect hyperarousal. A1/B1 differences are found between Nor and Mis, reflecting further sleep regulation (homeostasis) deregulations.

TABLE II. CAP DYNAMICS FEATURES WITH DIFFERENT ENCODINGS, AND KRUSKAL-WALLIS STATISTICS (ONLY FEATURES ALSO CHECKED WITH ANOVA AGAINST CAPTIME). I, N AND M REFER TO PSI, NOR AND MIS MEDIAN VALUES

Feature	Kruskal-Wallis Statistics			
	P	***Nor***	***PsI***	***Mis***
TAB_1 WE_{11}	0.0424 M<N	4.19 [3.07 4.65]	3.12 [1.96 3.33]	2.02 [1.55 3.45]
TAB_3 $nWEN_1$	0.0005 (M,I)>N	5.27 [4.83 5.48]	5.77 [5.51 6.03]	6.05 [5.83 6.33]
TAB_3 $nWEN_2$	0.0004 (M>N)	5.19 [4.83 5.41]	5.59 [5.46 5.89]	6.02 [5.86 6.31]
TAB_3 $nWEN_3$	0.0004 (M,I)>N	4.75 [4.51 4.91]	5.23 [5.05 5.47]	5.56 [5.28 5.80]
TAB_3 $nWEN_4$	0.0003 (M,I)>N	4.40 [4.04 4.59]	4.84 [4.78 5.16]	5.16 [4.97 5.29]
TAB_3 $nWEN_5$	0.0005 (M,I)>N	4.12 [3.64 4.27]	4.51 [4.40 4.71]	4.72 [4.57 4.90]
TAB_3 $nWEN_6$	0.0002 (M,I)>N	3.74 [3.50 3.86]	4.12 [4.00 4.21]	4.34 [4.16 4.37]
TAB_3 $nWEN_7$	0.0028 M>N	3.39 [3.10 3.77]	3.76 [3.52 3.97]	4.01 [3.83 4.10]
TAB_3 $nWEN_8$	0.0023 M>N	2.97 [2.75 3.32]	3.21 [3.02 3.52]	3.58 [3.41 3.63]
TAB_3 $nWEN_9$	0.0041 (M,I) > N	2.69 [2.39 2.87]	3.05 [2.95 3.14]	3.15 [2.94 3.31]
TAB_3 WEN_1	0.0230 I>N	0.27 [0.22 0.28]	0.30 [0.28 0.32]	0.30 [0.25 0.33]
TAB_3 WEN_2	0.0056 I>N	0.34 [0.32 0.38]	0.43 [0.40 0.44]	0.42 [0.35 0.45]
TAB_3 SD1	5e-005 M,I >N	0.21 [0.17 0.22]	0.26 [0.25 0.29]	0.34 [0.31 0.40]
TAB3 SD2	1.7e-004 M,I >N	0.21 [0.18 0.24]	0.29 [0.24 0.32]	0.34 [0.31 0.40]
TAB_A WE_7	0.0433 M<N	12.95 [12.46 15.31]	10.46 [9.2 12.84]	9.97 [8.64 11.24]
TAB_A $nWEN_9$	0.0257 M>N	2.89 [2.75 3.19]	3.16 [2.83 3.29]	3.25 [3.24 3.34]
TAB_A SD1	9e-005 M>N	0.78 [0.72 0.84]	0.96 [0.92 1.06]	1.22 [1.06 1.33]
TAB_A SD2	2.6e-004 (M,I) >N	0.87 [0.81 0.91]	1.07 [1.02 1.17]	1.29 [1.12 1.41]
XWm_{13}	0.0070 M>N	0.16 [0.14 0.17]	0.23 [0.17 0.26]	0.43 [0.27 0.48]
XWp_{13}	0.0377 M>N	0.02 [0 0.038]	0.039 [0.03 0.05]	0.047 [0.03 0.06]
WCm_{13}	0.0019 M>N	0.18 [0.14 0.19]	0.22 [0.20 0.25]	0.36 [0.26 0.38]

Moving beyond simple rates, Table II presents the CAP dynamics features that present a difference among the three groups (Kruskal-Wallis test shows that the three groups do not have the same median). Only the features that also present a statistical different (with ANOVA) when CAPtime is introduced as a second factor are presented. The rationale behind that is to filter out the features that their group values only reflect the CAPtime increase with insomnia, as various features could be affected by the increase of CAP activity. The main findings of this three-group analysis are following.

Both insomnia groups differ from normal in TAB_3 encoding (A3/B3 events) normalised wavelet entropy for scales <=6, short and long term variability (SD1 and SD2), and in TAB_A SD2, i.e. long range variability of all events. Additionally, Mis presents lower TAB_1 wavelet energy than

Nor, and higher wavelet complexity in many scales in TAB_3. Bigger SD1 variability of Mis in TAB_A, may suggest that alterations among series of events is more variable.

Finally, regarding cross-wavelet and coherence (XWm_{13}, XWp_{13} and WCm_{13}), both the magnitude of XWT and coherence is bigger in insomnia, and especially Mis, which suggests that at least in some scales, A1 and A3 events occur close by, in a more synchronized manner, than in normal sleep. An interesting finding is the bigger mean crosswavelet phase, showing a lead of A3 events in bigger scales (see Fig.1), which suggests that that A1 may occur as a response to A3 events in insomnia.

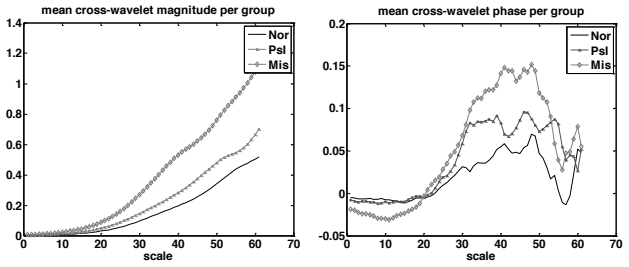

Figure 1. TAB_1-TAB_3 crosswavelet mean magnitude and phase per group.

The most important features (ranked by p value) that present differences between PsI and Mis are presented in Table III. It has to be noted that while CAPrate is similar, the overall CAPtime is increased in Mis. A general observation drawn from these results is that the TAB_A encoding, which incorporates all subtype events, presents most of the differences, with increased complexity and variability in Mis. The A1-A3 wavelet coherence shows also that the two subtypes may occur in proximity, or at least in similar and close temporal patterns in Mis, while they are more decorrelated in PsI (and in Nor).

TABLE III. MOST IMPORTANT DIFFERENCES BETWEEN MIS AND PSI

Feature	RankSum Statistics		
	p	***PsI***	***Mis***
TAB_A $nWEN_2$	0.0036	6.258 [6.173 6.463]	6.709 [6.486 6.933]
TAB_A SD1	0.0057	0.962 [0.928 1.061]	1.227 [1.067 1.330]
TAB_3 SD1	0.0091	0.268 [0.254 0.290]	0.342 [0.319 0.400]
TAB_1 $nWEN_8$	0.0113	3.293 [3.100 3.388]	3.641 [3.557 3.772]
TAB_A $nWEN_1$	0.0113	6.388 [6.301 6.643]	6.740 [6.565 6.913]
CAPtime	0.0140	8560 [6749 9843]	11085.5 [8809 13424]
WCOHm	0.0172	0.225 [0.206 0.259]	0.361 [0.261 0.389]

IV. DISCUSSION

This work explored a series of methods to compare Sleep State Misperception insomnia and Psychophysiological insomnia with normal sleep, in terms of sleep macrostructure and microstructure, i.e. CAP components. The sequence of activations of different subtypes were encoded as timeseries, on which statistical, variability as well as times-scale analysis was performed. A series of features were found that separate the two types of insomnia from normal sleep. Increase of A3/B3 events and their complexity was a common factor of insomnia, probably related to the hyperarousal. Sleep State Misperception insomnia, like psychophysiological insomnia, has been associated with increased physiological activation in previous studies [10]. As a matter of fact, findings related to sleep misperception revealed more intense CAP rate differences than in Psychophysiological insomnia, A1 subtype differences (homeostasis), and also findings which suggest a different linking of the different activation subtypes.

This study tackled the different CAP dynamics that seem to build the normal of pathologic macrostructure. Still the methodology needs to be complemented with a more detailed association and causality between events at different scales (micro-macro structure events). Additionally, this work included solely analysis of CAP events, and sleep macrostructure for reference, but not analysis of EEG or heart rate signals, which could build further to this work.

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