Mutual Information Measures Applied to EEG Signals for Sleepiness Characterization

Umberto Melia*, Marc Guaita**, Montserrat Vallverdú*, Cristina Embid**, Isabel Vilaseca**, Manel Salamero**, Joan Santamaria**

*Dept. ESAII, Centre for Biomedical Engineering Research, Universitat Politècnica de Catalunya, Barcelona, Spain; email: umberto.melia@upc.edu, montserrat.vallverdu@upc.edu, pere.caminal@upc.edu.

** Multidisciplinary Sleep Disorders Unit, Hospital Clinic de Barcelona, IDIBAPS, Barcelona, Spain.

Total word count: 4994 words

ABSTRACT

Excessive daytime sleepiness (EDS) is one of the main symptoms of several sleep related disorders with a great impact on the patient lives. While many studies have been carried out in order to assess daytime sleepiness, the automatic EDS detection still remains an open problem. In this work, a novel approach to this issue based on non-linear dynamical analysis of EEG signal was proposed. Multichannel EEG signals were recorded during five Maintenance of Wakefulness (MWT) and Multiple Sleep Latency (MSLT) tests alternated throughout the day from patients suffering from sleep disordered breathing (SDB). A group of 20 patients with excessive daytime sleepiness (EDS) was compared with a group of 20 patients without daytime sleepiness (WDS), by analyzing 60-second EEG windows in waking state. Measures obtained from cross-mutual information function (CMIF) and auto-mutual-information function (AMIF) were calculated in the EEG frequency bands: δ, 0.1-4 Hz; θ, 4-8 Hz; α, 8-12 Hz; β, 12-30 Hz; total band TB, 0.1-45 Hz. These functions permitted a quantification of the complexity properties of the EEG signal and the non-linear couplings between different zones of the scalp. Statistical differences between EDS and WDS groups were found in β band during MSLT events (p-value<0.0001). WDS group presented more complexity than EDS in the occipital zone, while a stronger nonlinear coupling between occipital and frontal zones was detected in EDS patients than in WDS. In general, AMIF and CMIF measures yielded sensitivity and specificity above 80% and AUC of ROC above 0.85 in classifying EDS and WDS patients.

Keywords: Biomedical signal processing, Complexity theory, Electroncephalography, EEG, Excessive daytime sleepiness, Mutual information.

1. Introduction

Excessive daytime sleepiness (EDS) is a socially and clinically relevant problem. According to one current definition, EDS is “the presence of sleepiness in a situation when an individual would be expected to be awake and alert” [1, 2]. EDS is a common symptom that can have many different causes. EDS occurring at least 3 days per week has been reported in between 4% and 20.6% of the population, while severe excessive daytime sleepiness was reported at 5% [3].

Electroencephalogram (EEG) recordings provide insight into the changes in brain activity associated with various states of arousal from sleep to waking and is often used as the “gold standard” in the identification of states ranging from vigilant and alert to drowsy [4] or asleep. Changes in the frequency and amplitude of the EEG correlate directly with behavioral performance measures [5] and changes in alertness and awareness [6-9].

Several researchers have attempted to leverage these characteristics to develop EEG based drowsiness algorithms using EEG feature extractions [10], EEG power spectral density bandwidth comparisons [11,12], event related potentials latency increases [13], linear regression [14], artificial neural networks [15], and principal component analysis [16]. However these algorithms present methodologies and results of mixed quality and weakness as small sample size, lack of cross validation analysis (or other acknowledgement/accommodation of individual variance), task dependence/specificity, algorithm complexity and large number of channels required. Furthermore, since many features of EEG signals cannot be generated by linear models, it is generally argued that non-linear measures are likely to give more information than the ones obtained with conventional linear approaches.

In the last few years, nonlinear techniques have been used to comprehend complex dynamics of the underlying neurophysiological processes [17,18] and to detect nonlinear interactions [19]. The fundamental assumption of nonlinear techniques is that the EEG signal is generated by nonlinear deterministic processes with nonlinear coupling interactions between neuronal populations. Nonlinearity in the brain likely occurs, even at the cellular level [20], since the dynamical behavior of individual neurons is governed by threshold and saturation phenomena, large networks of interconnected neurons are likely candidates for self-organized criticality, which refers to large systems with local nonlinear interactions in which a slow build-up of some energy value is alternated with brief bursts of energy redistribution [21]. The most applied complexity measures found in the literature are attractor dimension [22], correlation dimension [23], Lyapunov exponent [24], fractal dimension [25] and sample entropy [25]. All complexity measures mentioned above depend upon the setting of estimation parameters, namely embedding dimension, time delay of phase space reconstruction, prediction time horizon, and partitioning signals. Assuming that the dimensional complexity of the nonlinear system that the EEG signals generate is expected to be between 5 and 10 [26,27], depending on the awake or sleeping states, the limit of the time series length was defined between 10^3 and 10^5 samples [28] or even above than 10^5 [29]. These suppose a large sample size of data, besides that, the limited length of EEG time series available for sleepiness characterization disallows general dimension estimation methods since many patients felt asleep in less than 60 s (corresponding to 10^3 samples when a sampling frequency of 128 Hz is considered). In contrast, mutual information function, which describes the amount of information of a signal with regard to a time shifted quantity can be constructed on short time series. For those reasons, mutual information measures represent suitable methodology in order to characterize excessive daytime sleepiness and represent a general method to detect both linear and nonlinear statistical dependences between time series. On the other hand, mutual information requires the estimation of probabilities from limited data and the limited EEG time series might affect the estimation of mutual information functions. However, considering that the low limit of the length for mutual information computation was fixed to about 500 samples [30], in previous works mutual information functions were estimated with time series with length between 10^3 and 10^4 samples [30-32].

The main goal of this work was to characterize two groups of patients with different levels of excessive daytime sleepiness by the analysis of EEG windows in waking state. A novel approach to this issue based on nonlinear signal processing techniques is proposed. Auto-mutual information function (AMIF) was used to describe the complexity of the EEG signals. Cross-mutual information function (CMIF) was applied between different EEG channels in order to assess brain connectivity. These techniques detect linear and nonlinear statistical dependencies between time series, whereas the more standard correlation function measures only their linear dependence. Thus, indexes based on CMIF assess dynamical coupling or information transmission between two systems and when applied to the EEG they may be postulated to be measures of functional connectivity [33,34]. The study was performed in patients suffering sleep disturbances that undergoing the maintenance of wakefulness test (MWT) and multiple sleep latency test (MSLT). In the clinical practice, the MWT and MSLT are frequently used as sleep disorder diagnostic tools. They measure the time elapsed to fall asleep (sleep latency) in a soporiferous situation when the subject is instructed not to fall asleep (MWT) or with the instruction to try to fall asleep (MSLT). In other words, the MWT measures the resistance to fall asleep whereas the MSLT measures the capacity to fall asleep [35-37].

2. Materials And Methods

2.1 EEG Database and Preprocessing

The analyzed database belongs to the Multidisciplinary Sleep Disorders Unit of the Hospital Clínic (Barcelona, Spain). From a series of 98 consecutive patients with symptoms of SDB, 2 groups of 20 patients were selected consecutively based on mean sleep latencies from a MWT-MSLT research protocol: excessive daytime sleepiness (EDS) group (MWT < 20min and MSLT < 8min) and without daytime sleepiness (WDS) group (MWT > 20min and MSLT > 8min). They were matched by age and gender. For each patient, 6 channels of EEG (F3,F4,C3,C4,O1,O2) referenced to linked earlobes (A1+A2)/2 were recorded at 256 Hz during the MWT and MSLT. The MSLT and MWT consisted of a series of five nap opportunities during the day beginning approximately one hour after morning awakening, starting with the MWT and alternating each other throughout the day. The MSLT is performed with the subject lying down in bed in a comfortable position in a dark and quiet room with explicit instruction to try to fall asleep and the MWT with subjects semi-recumbent in a bed and with the instruction to stay awake. If no sleep occurred MWT and MSLT trials were ended after 40 and 20 minutes respectively, or after unequivocal sleep, defined as three consecutive epochs of stage 1 sleep, or one epoch of any other stage of sleep. Objective daytime sleepiness was measured from sleep latency defined as time from lights out to the first epoch of unequivocal sleep on each test [35,38].

The preprocessing consisted of resampling each EEG channel at 128 Hz after the application of a FIR band pass filter of 50th order, with cut-off frequencies of 0.1-45Hz. Then, the EEG was segmented in 60 s sliding windows with step of 20 s calculated during the whole tests. The selected windows were filtered into the characteristic frequency bands of the EEG signal: δ, 0.1-4 Hz; θ, 4-8 Hz; α, 8-12 Hz; β, 12-30 Hz; total band TB, 0.1-45 Hz.

2.2 Mutual Information Functions

Mutual information (MI) can measure the nonlinear as well as linear dependence of two variables. It is a metric derived from Shannon's information theory to estimate the information gained from observations of one random event on another [39,40]. It can be regarded as a nonlinear equivalent of the correlation function. Usually, MI is measured between two different systems X and Y. Let X and Y be discrete random variables which take a finite number of possible values x_i and y_j with probabilities $P_x(x_i)$ and $P_y(y_j)$ respectively, $i = 1, 2, 3...n$ and $j = 1, 2, 3...n$, MI between X and Y is given by [39,40]

$$MI_{xy} = \sum_{ij} P_{xy}(x_i, y_j)\, log_2\left(\frac{P_{xy}(x_i, y_j)}{P_x(x_i)P_y(y_j)}\right) \qquad (1)$$

In order to assess the information transfer via a certain prediction time τ, y_j is replaced by $y_{j+\tau}$, with any time shift τ. This leads to the cross-mutual information function (CMIF) that can be considered as an information-theoretic analogue of the cross-correlation function applied to time series. CMIF measures the amount of information that is common in both signals and is defined as

$$CMIF\_Sh(\tau) = \sum_{x_i \in X} \sum_{y_{j+\tau} \in Y} P_{xy}(x_i, y_{j+\tau})\, log_2\left(\frac{P_{xy}(x_i, y_{j+\tau})}{P_x(x_i)P_x(y_{j+\tau})}\right) \tag{2}$$

CMIF function provides complexity measures and quantifies the coupling between the two signals depending on the time lag τ, reflecting the information transfer at different time scales.

On the other hand, auto-mutual information function (AMIF) (3) is calculated as the MI between two measurements x_i and $x_{i+\tau}$ taken from a single time series.

$$AMIF\_Sh(\tau) = \sum_{x_i \in X} \sum_{x_{i+\tau} \in X} P_{xx}(x_i, x_{i+\tau})\, log_2\left(\frac{P_{xx}(x_i, x_{i+\tau})}{P_x(x_i)P_x(x_{i+\tau})}\right) \tag{3}$$

AMIF function describes how the information of a signal (*AMIF* value at $\tau = 0$) decreases over a prediction time interval (*AMIF* values $\tau > 0$). In the case of a completely regular and deterministic signal, the *AMIF* would remain at the maximum value of $\tau = 0$ for all τ. In the case of an uncorrelated random signal, the *AMIF* would become zero for all τ apart $\tau = 0$. Increasing information loss is related to decreasing predictability, and increasing complexity of the signal [31].

CMIF and AMIF can be also defined from Rényi entropy as

$$CMIF\_Re_q(\tau) = \frac{1}{q-1} log_2 \sum_{x_i \in X} \sum_{y_{j+\tau} \in Y} \frac{P_{xy}{}^q(x_i, y_{j+\tau})}{P_x{}^{q-1}(x_i)P_y^{q-1}(y_{j+\tau})}) \tag{4}$$

$$AMIF\_Re_q(\tau) = \frac{1}{q-1} log_2 \sum_{x_i \in X} \sum_{x_{i+\tau} \in X} \frac{P_{xx}{}^q(x_i, x_{i+\tau})}{P_x{}^{q-1}(x_i)P_x^{q-1}(x_{i+\tau})}) \tag{5}$$

where q is the control parameter of Rényi entropy.

In equations (4-5), the largest probabilities most influence the $CMIF\_Re_q$ and $AMIF\_Re_q$ when $q>1$ and the smallest probabilities most influence the values of $CMIF\_Re_q$ and $AMIF\_Re_q$ when $0<q<1$. The $CMIF\_Re_q$ and $AMIF\_Re_q$ converge respectively to the Shannon CMIF and AMIF when $q \rightarrow 1$. In this work, different values of the control parameter of *Re* were taken into account: $q = \{0.1, 0.2, 0.5, 3, 5, 10, 30, 50, 100\}$.

The probabilities P_{xy}, P_x and P_y were constructed on the series x_i or y_j and their delayed series $x_{i+\tau}$ or $y_{j+\tau}$ for $\tau = \{1,2,\ldots,128\}$ samples. The amplitude range of the data series was quantized using 32 equidistant partitions. This made the maximum possible value of CMIF and AMIF equal to $\log_2 32 = 5$ bits.

CMIF was calculated between pairs of EEG channels located over frontal, occipital and central regions (F3-C3, F4-C4, C3-O3, C4-O4), between central and occipital regions (O1-C3, O2-C4), across the central line (O1-F3, O2-F4) and between all pairs of inter-hemispheric channels. AMIF was calculated for the six EEG channels and normalized by the maximum value (AMIF(0)).

In order to quantify and extract the essential information contained on CMIF and AMIF, several measures were defined with respect to the delay τ: mean (*m*), first relative maximum (*maxL*), rate of decrease (*RDec*) [32], and first derivative (*FD*). The *FD* measure was calculated as the difference between the AMIF(0) and the AMIF(1), similarly *FD* measure for CMIF was calculated as the difference between the absolute maximum of the CMIF and the CMIF at subsequent τ.

As an example, Figure 1 shows the function $AMIF\_Re_3(\tau)$ averaged with respect to all MWT and MSLT of an EDS and WDS single patient, calculated in β band of O2 channel. Since AMIF is symmetric function, negative delays are not displayed. From the same patients, $CMIF\_Re_{30}(\tau)$ averaged with respect to all MWT and MSLT, calculated in β band between C4-O2 channels, is shown in Figure 2. AMIF profile (Figure 1) exhibited transient oscillations and then decreased to nonzero stable values after a certain time delay. This value is higher in MWT than in MSLT for the patient in the WDS group and lower in MWT than in MSLT for the patient in EDS group, denoting different complexity behavior in the two types of trials. Therefore, EEG in β band presents higher complexity during MWT for the EDS patient whereas it presents higher regularity during MWT test for the WDS patient. CMIF profile (Figure 2) also exhibited transient oscillation and then decreased gradually round nonzero stable values after a certain time delay. These values and the peak are different between MWT and MSLT for the EDS and WDS patient, denoting different nonlinear coupling behavior between C4-O2 channels in β band. The MWT of the EDS patient presents less coupling whereas the signals from WDS patient present more coupling in MWT.

2.3 Traditional EEG Measures

In order to compare the AMIF measures with temporal and frequency linear measures, the following traditional measures were calculated in each channel:

- Standard deviation (*std*) of the EEG windows filtered in each band.
- Power spectral density (*PSD*) for each EEG window in TB band using the Welch method.

- Spectral power (P_δ , P_θ , P_α , P_β) as the area under the PSD curve in each band normalized by the total PSD area.
- Mean frequency (*mF*) in each band as the centroid of the PSD curve.
- Spectral edge frequencies *SEF50*, *SEF75* and *SEF90* in each band. The *SEFx* was calculated as the frequency below which x % of the total EEG spectral power is located.
- Autocorrelation function (*Ac*)

In order to compare the CMIF measures with temporal and frequency linear measures, the following traditional measures were calculated between all the combinations of the channels:

- Mean value, maximum value, *mF* and *SEF50*, *SEF75* and *SEF90* of the coherence function (*Cf*) in each band.
- Cross-correlation function (*Cc*)

2.4 Analysis of the EEG Measures

To pursue our goal, different studies were performed comparing the proposed measures calculated from EDS patients and from WDS patients. Firstly, the mean value of the measures obtained from each of the first 60 s window at the beginning of all MWT and also the mean value of the measures obtained from each of the first 60 s window at the beginning of all MSLT was calculated for each patient (Study 1) in order to find the measures that can best characterize the two groups. Then, in order to assess if the previous results were improved by the changes that two different situations (MWT and MSLT) produced in a single measure in the two groups (EDS and WDS), multi-variable discriminant functions (Study 2) were built by combining a measure of Study 1 calculated in MWT with the equivalent measure calculated in MSLT. Finally, measures calculated in each of the 60 s sliding windows during the entire tests (MWT and MSLT) were analyzed, in order to analyze the behavior of the non-linear measures in the entire recording as sleep onset approaches (Study 3).

2.5 *Statistical Analysis*

A non-parametric test, Mann-Whitney U-test, was applied and a significance level p-value <0.05 was taken into account. Measures that satisfy this condition were considered for building a discriminant function. The leaving-one-out method was performed as validation method. Sensitivity (*Sen*) and specificity (*Spe*) were calculated for testing the performance of the measures. In this way, the proportion of patients in EDS group correctly classified were counted by *Sen* and the proportion of patients in WDS group correctly classified by *Spe*.

Also the area under ROC curve (*AUC*) was used to test the performance of the measures. The ROC curve was computed for the results of the predictions calculated with logistic regression classification using a generalized linear model. The model was built by fitting a generalized linear regression of the predicted classes on the measures, using normal distribution [41].

3. Results

3.1 Analysis of the first 60-second window at the beginning of MSLT and MWT

Table 1 shows the AMIF measures that have given the best performances for Study 1. It can be noted that the best results to differentiate the alert from the sleepy groups during the first minute of the tests, with the patient still awake, were found for *FDAMIF_Re3(β)* in O1 and O2 channel, yielding a $Sen \geq 60$, $Spe>75$ and $AUC>0.75$ in both MWT and MSLT tests (table 1). Figure 3a shows the evolution of *AUC* calculated on *FDAMIF(β)* as a function of the control parameter q in all the channels. It can be observed an increasing of *AUC* for $1<q<10$ in all channels. Thus, it can be deduced from table 1 and Figure 3a that occipital region of the brain (O1 and O2) gave the best discrimination performance with a control parameter value q=3. Figure 3b and 3c show the averaging of *AMIF* (τ) function in O2 channel calculated with different q values with respect to all MWT and MSLT of all EDS and WDS patients respectively. It can be noted that the increasing of the parameter q is associated with lower decay and higher relative maximum at low τ values combined to a higher value at higher τ. In this way, since *FDAMIF_Re3(β)* in the O2 channel resulted to be the best AMIF measure in this Study, individual analysis of MSLT and MWT trials was performed with that measure calculated from one 60 s window at the beginning of each MWT (MWT1, MWT2, MWT3, MWT4, MWT5) and MSLT (MSLT1, MSLT2, MSLT3, MSLT4, MSLT5). Table 2 and Figure 4 show the *Sen*, *Spe, AUC* and the mean value in each MWT and MSLT of *FDAMIF_Re3(β)* in the O2 channel. As it can be observed in Figure 4, the behavior of EEG β band of EDS patients presents less complexity than WDS in all MSLT and MWT.

CMIF measures that gave the best statistical performances in Study 1 are shown in Table 3. The values of CMIF measures indicate that nonlinear coupling in β band between occipital (O1, O2) and frontal (F3, F4) regions is stronger for EDS patients than WDS in MSLT tests. The behavior of $CMIF\_Re_{30}(\tau)$ between C4-O2 channels in β band, averaged with respect to all MWT or MSLT (Figure 5) confirms that EDS group presents more nonlinear coupling than WDS group at different time scale in MSLT. In general, the values of the parameter q influenced in a different way the results of AMIF and CMIF: *Sen*, *Spe* and *AUC* of AMIF increased for $1<q<10$, while the discriminatory capability of CMIF was improved for $q>10$. However, it should be pointed out that CMIF measures do not improve the results of AMIF. Furthermore, we found that none of CMIF measures were able to statistically discriminate EDS and WDS patients in any individual MWT and MSLT trials, since *Sen* and *Spe* were lower than 60%.

Table 4 presents the AMIF and CMIF measures with the highest *Sen*, *Spe* and *AUC* in Study 2. This study was performed building a multi-variable discriminant function between measures in MWT with their equivalent in MSLT. As an example, Figure 6 shows the scatter plots of MWT with respect to MSLT of the values of $FDAMIF\_Re_3(\beta)$ in O1 channel and $FDAMIF\_Re_3(\beta)$ in O2 channel and Figure 7 shows the scatter plots of MWT with respect to MSLT of the values of $FDCMIF\_Re_{10}(\beta)$ between O2-F3 and $mCMIF\_Re_{30}(\beta)$ between C4-O2.

It can be observed that in Study 2 only CMIF measures improved the discrimination performance compared with Study 1. In this way, the best discrimination performance was obtained in Study 2 between C4-O2 by $mCMIF\_Re_{30}(\beta)$. Thus, Figure 8a shows the values of *AUC* calculated on $mCMIF(\beta)$ between C4-O2 channels as a function of the control parameter q. It can be observed an increasing of *AUC* till a fix value reached approximately for q=30. Figures 8b and 8c show the averaging of $CMIF(\tau)$ function between C4-O2 calculated with different q values with respect to all MWT of all EDS and WDS patients, respectively. It can be noted that when q increases the maximum value and the minimum stable values of CMIF also increases. Analyzing the distribution of the values of *AUC* calculated on $mCMIFRe_{30}(\beta)$ between channels (Figure 9), it can be observed that the higher *AUC* values are obtained in the coupling between EEG channels from central and occipital area.

3.2 Analysis of Sleep Onset

In Study 3, in order to analyze the behavior of the non-linear measures in the entire recording as sleep onset approaches, we analyzed measures calculated in each of the 60 s sliding windows during the entire tests (MWT and MSLT). Figure 10 shows the evolution of $FDAMIF\_Re_3(\beta)$ in O2 channel calculated by sliding 60 s windows in steps of 20 s during all MWT and all MSLT for all the patients. In order to evaluate differences between groups due to the SO effect and to the changes along the wake-sleep transition, 600 s before the SO and 100s after the SO are represented, excluding the patients that did not fall asleep in a given nap. In this way, we focused on the moment of change that is common to the two groups. The continuous line represents the averaging of the measure, where EDS patients are represented in blue and WDS in red. Left panels (Figure 10a,c,e,g,i) contain the evolution for MWT and right panels (Figure 10 b,d,f,h,l) the evolution for MSLT. The trend of this measure along the time confirms the results that EDS patients present less complexity than WDS patients in O2 channel of β band. The results of statistical analysis between EDS vs. WDS patients for each window are shown by black squares and black triangles that indicate the time instants in which p-value<0.05 and *AUC*>0.75, respectively. Significant statistical differences occur for a high number of windows in waking state during all MSLT naps. It was found that in MSLT2, MSLT3 and MSLT5 all *Sen*, *Spe*, and *AUC* were above 75% when the mean value of the measure in all the windows was taken into account.

3.3 Traditional Measures

Table 5 shows the results of the best traditional measures in each of the study. In general, from table 5, it can be noted that EDS group presents higher coherence than WDS group between channel F4-O2 and F3-F4 during MWT. The power spectral in θ band in F3 channel in Study 1 during MWT5, where P_θ of EDS group is lower than WDS group, have different behavior respect Study 3 during MWT1, where P_θ of EDS group is higher than WDS group.

However all *Sen*, *Spe*, and *AUC* are never above 80%, 70% and 0.75 respectively.

4. Discussion

Nonlinear dynamics analysis was performed on EEG recorded in two groups of patients (EDS and WDS) who underwent MSLT and MWT tests. Several measures were calculated on AMIF and CMIF applied on 60 s EEG windows in the waking state, right at the beginning of the naps, in order to characterize the two groups.

It is well known that the transition from wakefulness into asleep is electrophysiologically characterized by the decrease in α and β activity in EEG and the beginning of synchronized activity, expressed by the increasing level of activity in the δ/θ ranges, by the disappearance of α rhythm and by a continuing decrease in the β band. This is followed by a uniformly increasing trend across the 1–16 Hz frequency range, while EEG power within the faster frequency range reaches its lowest point [42]. The progressive synchronization of the EEG is expressed by a centro-frontal prominence within the δ/θ

frequency range. This prevalence began about 60 s before sleep onset and lasted across the entire 5 min interval after sleep onset. In other words, the systematic prevalence of EEG power at the central brain site seems to indicate that it is the first one to synchronize its EEG oscillations, while the occipital scalp location is the last one [42]. Previous studies also evidence that the β band revealed a low level of EEG power that linearly decreases and is prevalent at the occipital scalp location; the highest EEG power in the α frequency range was found on the occipital area, but this prevalence progressively vanished, ending in coincidence with sleep onset [43].

In the present work different complexity behavior between EDS and WDS patients was found in β band in the occipital zones. AMIF results demonstrated that in waking windows this complexity is higher (p-value<0.005) in WDS group than EDS during MSLT (Table 2). In Figure 4, it can be denoted a different behavior of the non-linear measures along all the MWT and MSLT naps, while the WDS group presents changes in complexity behavior between MWT and MSLT, the EDS group maintains a low complexity for both MWT and MSLT. In Figure 10, it can be observed that for both EDS and WDS patients the complexity decreases with time with similar slope when approaching the sleep onset. In the MSLT, there are differences between groups during the previous minutes to the appearance of the SO, whereas after SO both groups reduce the complexity of the signal. Then, the differences between groups are reduced close to the SO that implies a reduction of the complexity of the β band in both groups. In the MWT nap, the complexity is lower in the groups EDS but statistically differences was only observed near the SO (from -100 s to +100 s), where the decrease of EDS complexity has a slope higher than the WDS.

A previous work showed that entering to sleep is accompanied by the loss of connectivity in anterior and posterior portions of the default-mode network and more locally organized global network architecture [44]. In the present work, this relation has been observed in CMIF results, denoting that the coupling is stronger in EDS patient than WDS during MSLT (p-value<0.005) in β band between the frontal and central (F4-C4), frontal and occipital (F3-O2), central and occipital (C4-O1) and also in occipital and inter-hemispheric (O1-O2) (Table 3). The results of Study 2 suggest that the interaction between the nonlinear coupling measures in MSLT with their equivalent in MWT help to improve the classification between EDS and WDS group (Table 4).

Our studies also confirm that the tendencies of *Sen*, *Spe* and *AUC* of the previous Studies calculated in a waking window at the beginning of each MWT and MSLT remain the same in all the windows during the all tests.

Comparing the results of the traditional temporal and frequency linear measures in table 5 with the AMIF and CMIF results in tables 1-4, it can be noted that in each study the best AMIF and CMIF measures have higher values of *Sen*, *Spe*, and *AUC* than the best traditional measures. This demonstrates the improvements of the proposed method due to the capability of mutual information functions of characterizing non-linear EEG features that traditional measures cannot detect. In general, the most remarkable results by both AMIF and CMIF in the discrimination of EDS and WDS patients were obtained in β band during MSLT. The best *Sen*, *Spe* and *AUC* were observed in AMIF measures applied on occipital region (O1 and O2) and in CMIF measures between inter-hemispheric channels (O2-F3, O1-F4), central and occipital regions (O2-C4) and across the central line (O1-F3, O2-F4). Both AMIF and CMIF results stand out the benefit of the nonlinear approach and demonstrate that mutual information measures represent useful tools in the sleepiness characterization providing significantly statistical difference between EDS and WDS patient.

In the current work, we took into account EEG during wakefulness in people with and without sleepiness and focused only on stage I sleep rather than in the other stages. Other works have analyzed the EEG during the process of entering sleep, but taking sleep onset as the time of the first sleep spindle [42, 43], which is much later than we considered. Our methodology could help detect sleep onset in an automatic way so well as standard criteria (visual analysis), for routine diagnostic MSLT or MWT but also to detect and warn when someone is at risk of falling asleep, as a drowsiness detectors in cars as a system to help driving safer.

5. Conclusions

The complexity and the non-linear dynamic of the EEG signal of patients with different degrees of sleepiness were described by AMIF measures. In general, WDS group presents more complexity in β band than EDS group in all the EEG channels during MSLT. The non-linear coupling between different scalp areas of the EEG signal was described by CMIF measures. Non-linear coupling in β band between different scalp zones are stronger in EDS patient than WDS.

The AMIF measures yield the classification performances *Sen*>80%, *Spe*>80% and *AUC*>0.85. Furthermore, the classification performances of CMIF increase by combining measures of MWT with their equivalent of MSLT yield *Sen*=80%, *Spe*=100% and *AUC*=0.938.

In conclusion, AMIF and CMIF measures applied to a 60 s window of EEG permit to characterize if patients are suffering EDS with significantly high discrimination performances.

Acknowledgment

This work was supported within the framework of the CICYT grant TEC2010-20886, the FIS PI07/0318 to MS (co-financed by FEDER) and the Research Fellowship Grant FPU AP2009-0858 from the Spanish Government.

Author Declaration

Competing interests: None declared

Funding: None

Ethical approval: The study received approval from the Ethics Committee of Hospital Clinic de Barcelona and all the patients signed informed consent.

References

[1] Arand D, Bonnet M, Hurwitz T, Mitler M, Rosa R, Sangal RB, The clinical use of the MSLT and MWT Sleep 2005;28(1):123-44.

[2] Lombardi C, Parati G, Cortelli P, Provini F, Vetrugno R, Plazzi G, Vignatelli L, Daytime sleepiness and neural cardiac modulation in sleeprelated breathing disorders. Journal of sleep research 2008;17(3):263-270.

[3] Ohayon MM, From wakefulness to excessive sleepiness: what we know and still need to know Sleep Med Rev 2008; 12(2): 129–141.

[4] Santamaria J, Chiappa KH, The EEG of drowsiness in normal adults. Journal of clinical Neurophysiology 1987; 4(4):327-382.

[5] Jung T, Makeig S, Estimating levels of alertness from EEG. Proc IEEE- EMBS Conf 1994;pp 1103-1104.

[6] Makeig S, Inlow M, Lapses in alertness: coherence of fluctuations in performance and EEG spectrum. Electroencephalography and Clinical Neurophysiology 1993;86(1):23–35.

[7] Andrews-Hanna JR, Reidler JS, Huang C, Buckner RL, Evidence for the default networks role in spontaneous cognition. Journal of Neurophysiology 2010;104:322–335.

[8] Gusnard DA, Akbudak E, Shulman GL, Raichle ME, Medial prefrontal cortex and self-referential mental activity: Relation to a default mode of brain function. Proceedings of the National Academy of Sciences of the United States of America 2001;98:4259–4264.

[9] Vanhaudenhuyse A, Demertzi A, Schabus M, Noirhomme Q, Bredart S, Boly M, Laureys S, Two distinct neuronal networks mediate the awareness of environment and of self. Journal of Cognitive Neuroscience 2010;1:1–9.

[10] Johnson RR, Popovic PD, Olmstead RE, Stikic M, Levendowski DJ, Berka C, Drowsiness/alertness algorithm development and validation using synchronized EEG and cognitive performance to individualize a generalized model. Biological Psychology 2011;87(2):241–250.

[11] Lin CT, Pal NR, Chuang CY , Jung TP , Ko LW, Liang SF, EEG-based subject and session-independent drowsiness detection: an unsupervised approach. Neural Networks, IJCNN (IEEE World Congress on Computational Intelligence). IEEE International Joint Conference 2008;pp 3448-3454.

[12] Swarnkar V, Abeyratne U, Hukins C, Objective measure of sleepiness and sleep latency via bispectrum analysis of EEG. Medical & Biological Engineering & Computing 2010;48(12):1203-1213.

[13] Smith ME, McEvoy LK, Gevins A, The impact of moderate sleep loss on neurophysiologic signals during working-memory task performance. Sleep 2002;25(7):784–794.

[14] Chiou JC, Ko LW, Lin CT, Hong CT, Jung TP, Liang SF, Jeng JL, Using novel MEMS EEG sensors in detecting drowsiness application. Proc of Biomedical Circuits and Systems Conference London 2006;pp 33-36.

[15] Subasi A, Erçelebi E, Classification of EEG signals using neural network and logistic regression. Comput Methods Programs Biomed 2005;78(2):87-99 .

[16] Fu J, Li M, Lu BL, Detecting drowsiness in driving simulation based on EEG. Autonomous Systems–Self-Organization, Management, and Control 2008;21-28.

[17] Jeong J, EEG dynamics in patients with Alzheimer's disease. Clin Neurophysiol 2004;115:1490–1505.

[18] Sabeti M, Katebi S, Boostani R, Entropy and complexity measures for EEG signal classification of schizophrenic and control participants. Artificial intelligence in medicine 2009;47(3):263-274.

[19] Alonso JF, Mananas MA, Romero S, Hoyer D, Riba J, Barbanoj MJ, Drug effect on EEG connectivity assessed by linear and nonlinear couplings. Human brain mapping 2010;31(3):487-497.

[20] Andrzejak RG, Lehnertz K, Moormann F, Rieke C, David P, Elger CE, Indications of nonlinear deterministic and finite-dimensional structures in time series of brain electrical activity: dependence on recording region and brain state. Phys Rev 2001;64(6):061907.

[21] Stam CJ, Nonlinear dynamical analysis of EEG and MEG: review of an emerging field. Clin Neurophysiol 2005;116:2266–2301.

[22] Pradhan N, Sadasivan PK, The nature of dominant Lyapunov exponent and attractor dimension curves of EEG in sleep. Computers in biology and medicine 1996;26(5):419-428.

[23] Acharya UR, Faust O, Kannathal N, Chua T, Laxminarayan S, Non-linear analysis of EEG signals at various sleep stages. Computer Methods and Programs in Biomedicine 2005;80(1):37-45.

[24] Fell J, Röschke J, Beckmann P, Deterministic chaos and the first positive Lyapunov exponent: a nonlinear analysis of the human electroencephalogram during sleep. Biological cybernetics 1993;69(2):139-146.

[25] Chouvarda I, Rosso V, Mendez MO, Bianchi AM, Parrino L, Grassi A, Terzano M, Cerutti S, Assessment of the EEG complexity during activations from sleep. Computer methods and programs in biomedicine 2011;104(3):e16-e28.

[26] Shen Y, Olbrich E, Achermann P, Meier P F, Dimensional complexity and spectral properties of the human sleep EEG. Clinical Neurophysiology 2003;114(2):199-209.

[27] Pereda E, Gamundi A, Rial R, Gonzalez J , Non-linear behaviour of human EEG: fractal exponent versus correlation dimension in awake and sleep stages. Neuroscience letters 1998;250(2):91-94.

[28] Eckmann J P, Ruelle D, Fundamental limitations for estimating dimensions and Lyapunov exponents in dynamical systems. Physica D: Nonlinear Phenomena 1992;56(2):185-187.

[29] Theiler J, Estimating fractal dimension. JOSA A 1990;7(6):1055-1073.

[30] Hoyer D, Friedrich H, Frank B, Pompe B, Baranowski R, Żebrowski J J, Schmidt H, Autonomic information flow improves prognostic impact of task force HRV monitoring. Computer methods and programs in biomedicine 2006;81(3):246-255.

[31] Hoyer D, Pompe B, Chon KH, Hardraht H, Wicher C, Zwiener U, Mutual information function assesses autonomic information flow of heart rate dynamics at different time scales. IEEE Trans Biomed Eng 2005,52(4):584–592.

[32] Jeong J, Gore JC, Peterson BS, Mutual information analysis of the EEG in patients with Alzheimer's disease. Clin Neurophysiol 2001;112:827–835.

[33] Hoyer D, Leder U, Hoyer H, Pompe B, Sommer M, Zwiener U, Mutual information and phase dependencies: measures of reduced nonlinear cardiorespiratory interactions after myocardial infarction. Medical Engineering & Physics 2002;24:33–43.

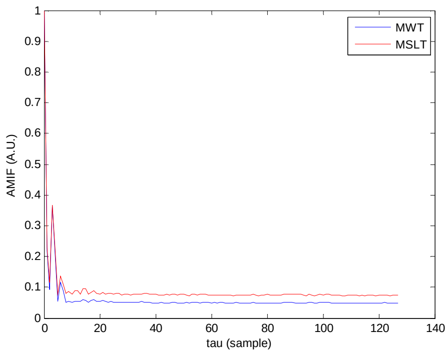
[34] Alonso JF, Mañanas MA, Hoyer D, Topor ZL, Bruce EN, Evaluation of respiratory muscles activity by means of cross mutual information function at different levels of ventilatory effort. IEEE Transactions On Biomedical Engineering 2007;54(9):1573-1582.

[35] Carskadon MA, Dement WC, Mitler MM, Roth T, Westbrook PR, Keenan S Guidelines for the Multiple Sleep Latency Test (MSLT): a standard measure of sleepiness. Sleep 1986;9(519–524).

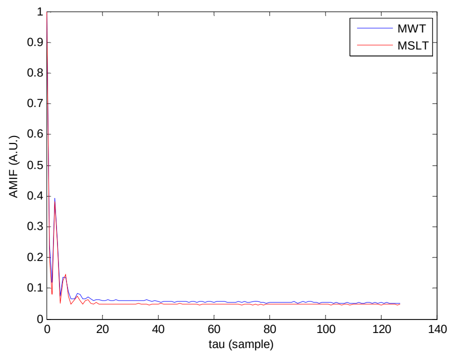
[36] Richardson GS, Carskadon MA, Flagg W, Van den Hoed J, Dement WC, Mitler MM, Excessive daytime sleepiness in man: multiple sleep latency measurement in narcoleptic and control subjects. Electroencephalogr Clin Neurophysiol 1978;45(5):621–627.

[37] Thorpy MJ, Westbrook P, Ferber R, Fredrickson P, Mahowald M, Perez-Guerra F, Reite M, Smith P, The clinical use of the Multiple Sleep Latency Test. Sleep 1992;15:268–276.
[38] Doghramji K, Mitler MM, Sangal RB, Shapiro C, Taylor S, Walsleben J, et al A normative study of the maintenance of wakefulness test (MWT) Electroencephalogr Clin Neurophysiol 1997;103:554–62.
[39] Plattard D, Soret M, Troccaz J, Vassal P, Giraud Champleboux JY, Artignan GX, Bolla M, Patient setup using portal images: 2D/2D image registration using mutual information. Computer Aided Surgery 2000;5(4):246–262.
[40] Wells III WM, Viola P, Kikinis R, Multi-modal volume registration by maximization of mutual information. Medical Robotics and Computer Assisted Surgery 1995;1:55–62.
[41] McCullagh P , Nelder JA, Generalized Linear Models New York: Chapman & Hall, 1990
[42] De Gennaro L, Ferrara M , Bertini M, The boundary between wakefulness and sleep: quantitative electroencephalographic changes during the sleep onset period. Neuroscience 2001;107(1):1-11.
[43] De Gennaro L, Vecchio F, Ferrara M, Curcio G , Rossini PM, Babiloni C, Antero-posterior functional coupling at sleep onset: Changes as a function of increased sleep pressure. Brain Research Bulletin 2005;65:133–140.
[44] Van Someren EJW, Modulation of the brain's functional network architecture in the transition from wake to sleep. Slow brain oscillations of sleep, resting state and vigilance 2011;193:277.

Figures:

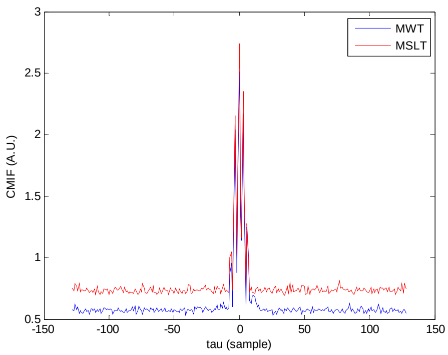


(a)

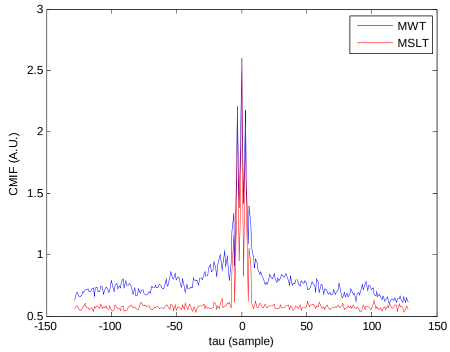


(b)

Fig. 1. Channel O2, β band: Averaging of function $AMIF\_Re_3(\tau)$ with respect to all MWT and MSLT of (a) a single patient of EDS group and (b) a single patient of WDS group.

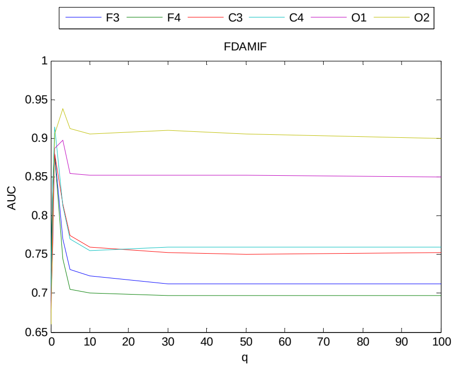


(a)

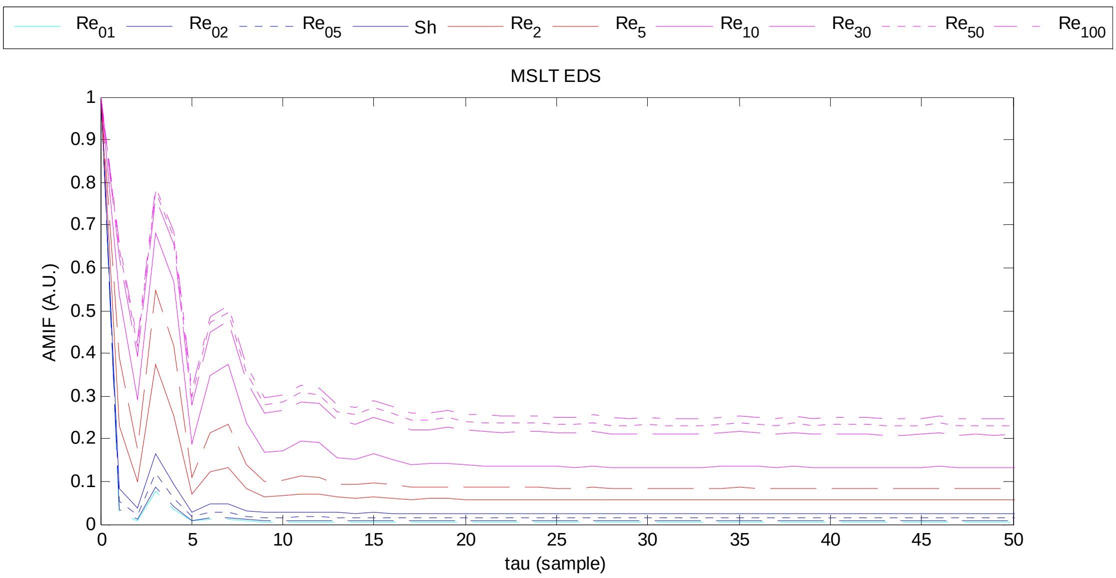


(b)

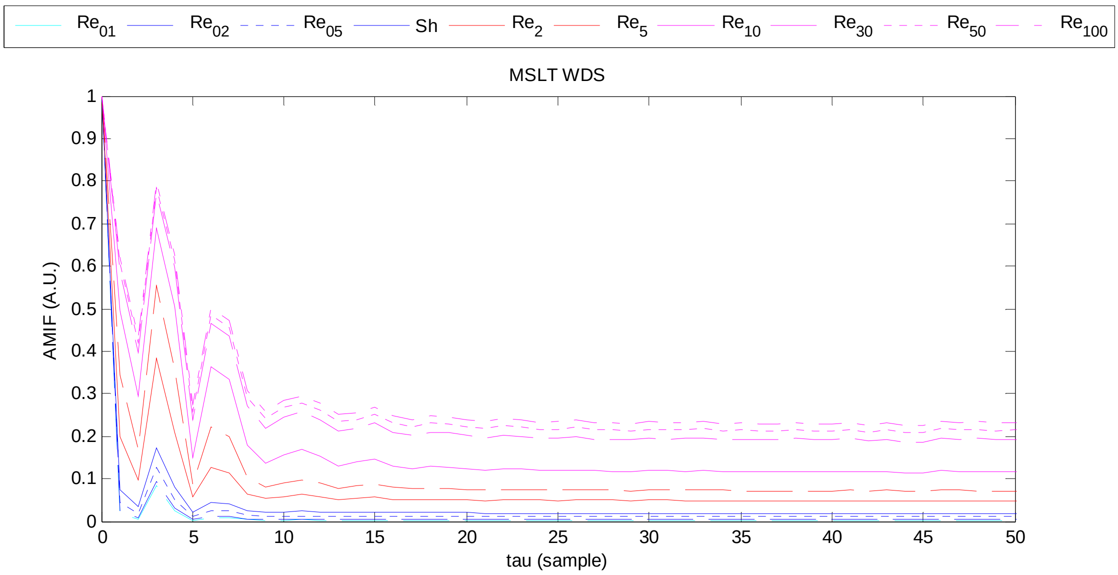
Fig. 2. Channels C4-O2, β band: Averaging of function $CMIF\_Re_{30}(\tau)$ with respect to all MWT and MSLT of (a) a single patient of EDS group and (b) a single patient of WDS group.



(a)



(b)



(c)

Fig. 3. Influence of parameter q on *AUC* values and *AMIF* functions: (a) values of AUC with respect to control parameter q calculated on $FDAMIF(\beta)$ in all channels,(b) averaging of $AMIF$ (τ) function in O2 channel with respect to all MSLT of all EDS patients calculated with different q values, (c) averaging of $AMIF$ (τ) function in O2 channel with respect to all MSLT of all WDS patients calculated with different q values.

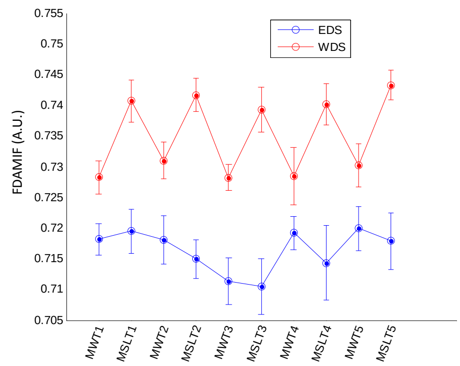


Fig. 4 Mean value and standard error of $FDAMIF\_Re_3(\beta)$ in O2 channel.

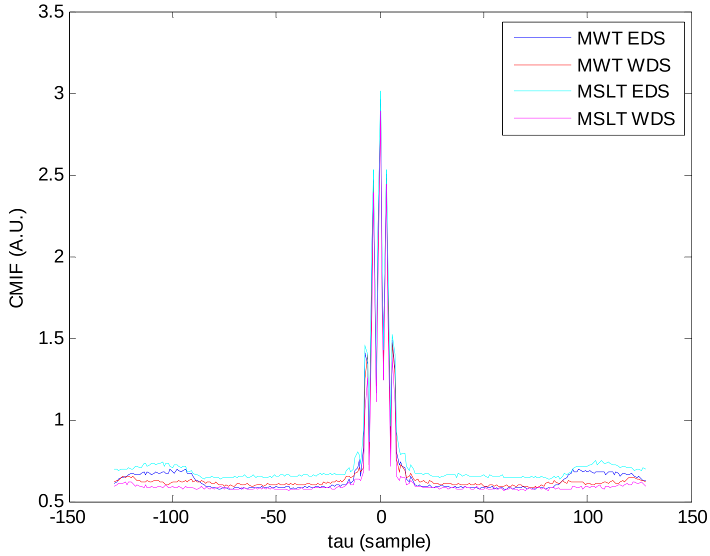
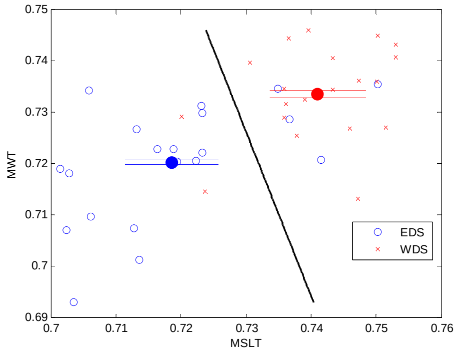
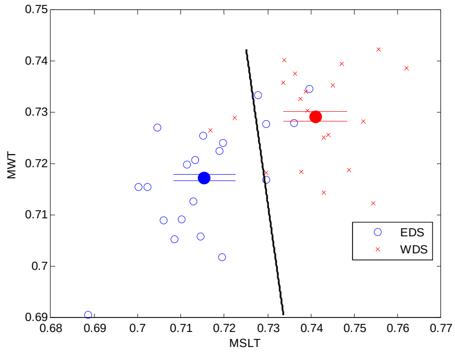


Fig. 5. Channels C4-O2, β band: Averaging of function $CMIF\_Re_{30}(\tau)$ with respect to all MWT and MSLT of all EDS and WDS patients.

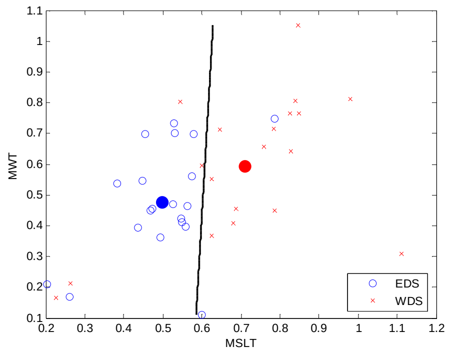


(a)

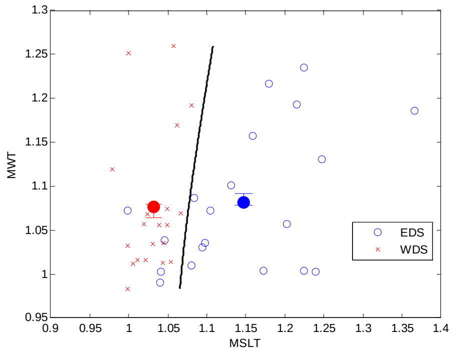


(b)

Fig. 6. Study 2, multivariable function between MWT and MSLT: Scatter plots of MWT with respect to MSLT: mean values and centroids of *FDAMIF_Re*$_3$*(β)* (a) in O1 channel and (b) in O2 channel.

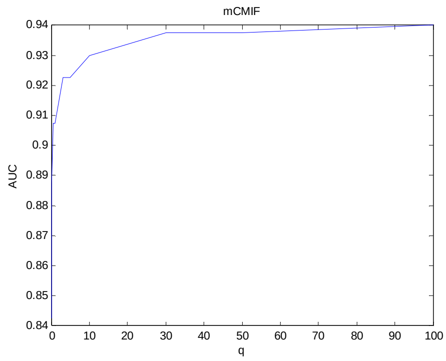


(a)

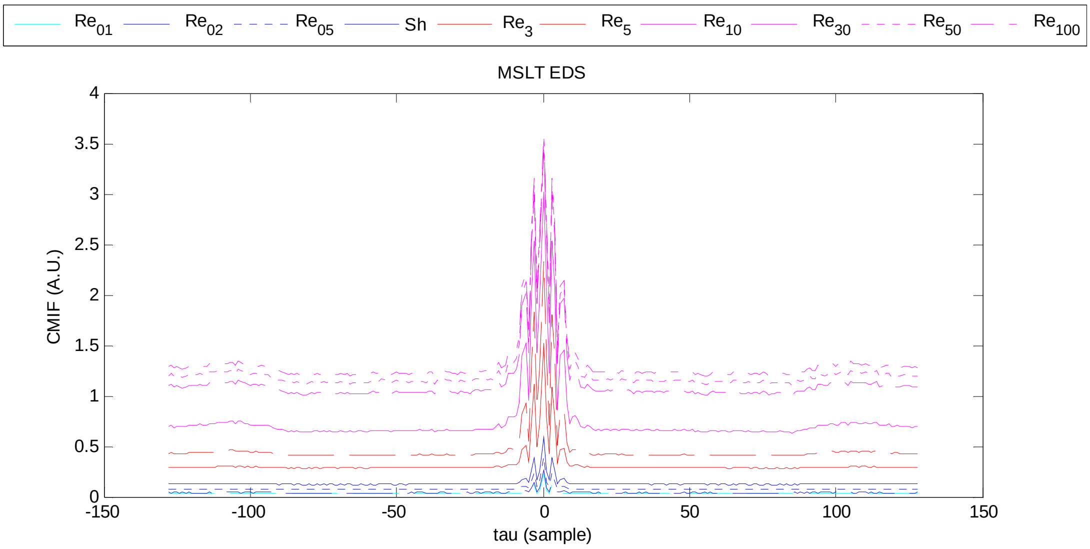


(b)

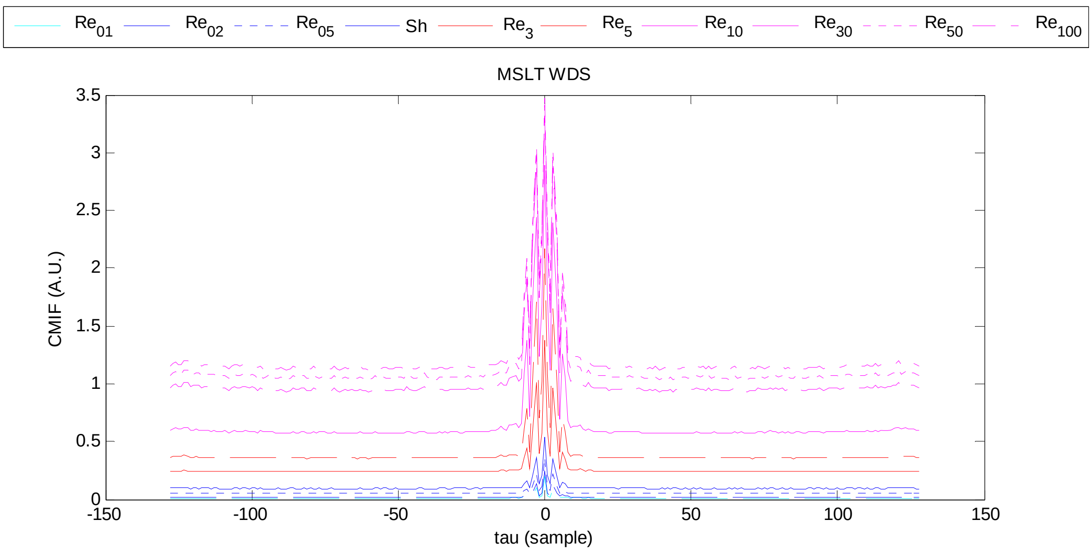
Fig. 7. Study 2, multivariable function between MWT and MSLT: Scatter plots of MWT with respect to MSLT: mean values and centroids of (a) *FDCMIF_Re*$_{10}$*(β)* between F3-O2 and (b) *mCMIF_Re*$_{30}$ *(β)* between C4-O2.



(a)



(b)



(c)

Fig. 8. (a) Values of *AUC* with respect to q of *mCMIF* (β) between C4-O2, (b) averaging of *CMIF* (τ) function between C4-O2 with respect to all MWT of all EDS patients calculated with different q values, (c) averaging of *CMIF* (τ) function between C4-O2 with respect to all MSLT of all WDS patients calculated with different q values.

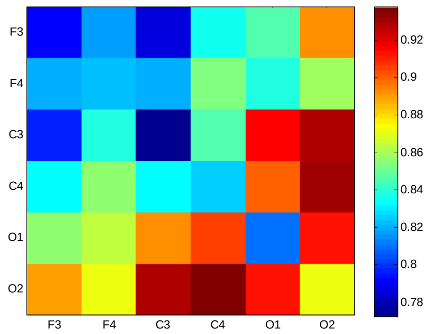
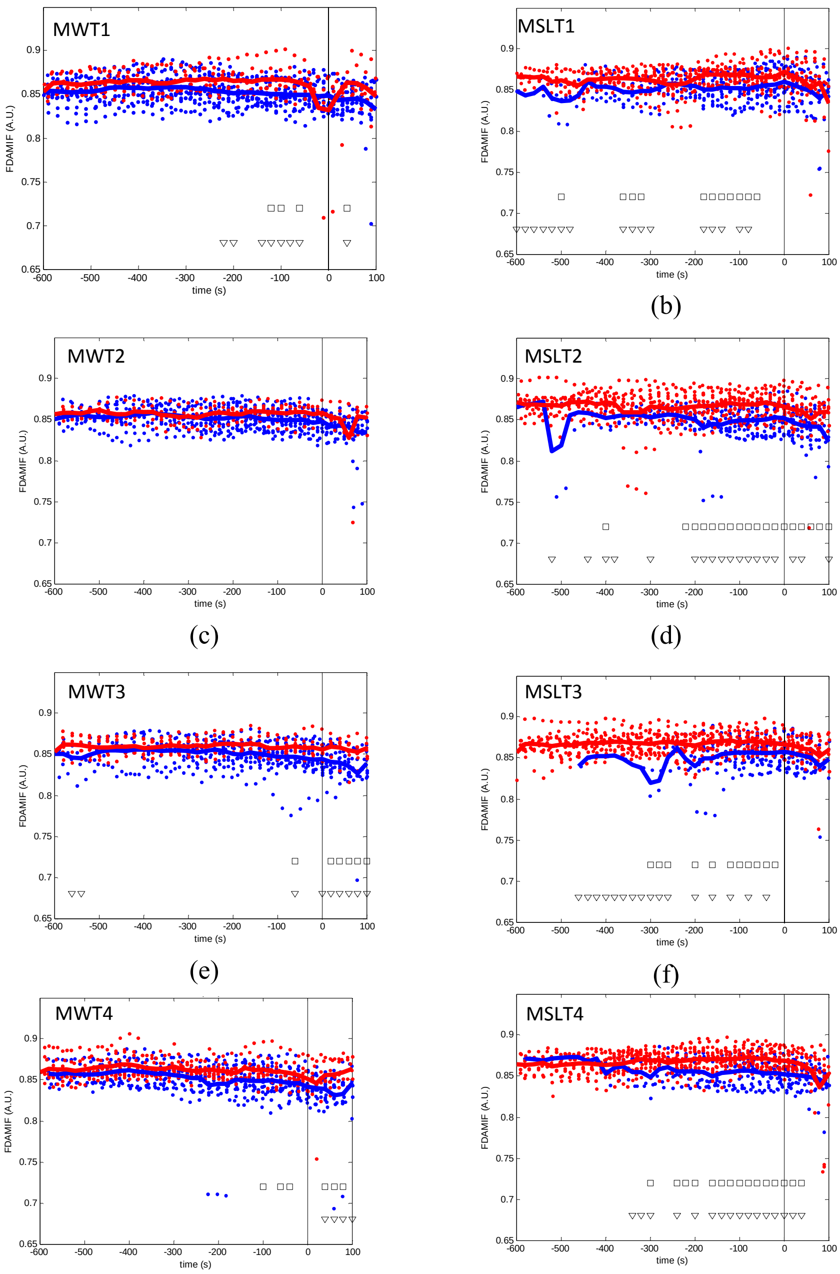


Fig. 9. Study 2, multivariable function between MWT and MSLT: distribution of AUC of $mCMIFRe_{30}$ (β) in each coupled channel.



(b)

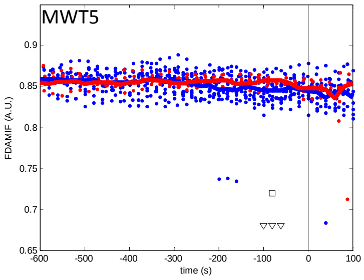
(c)

(d)

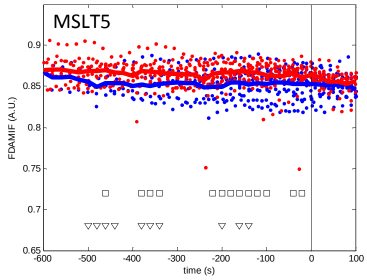
(e)

(f)

(h)



(i)



(l)

Fig. 10. Study 3: Evolution of *FDAMIF_Re₃(β)* in O2 of all the patients , EDS patients in blue and WDS patients in red, calculated by sliding 60 s windows in steps of 20 s during (a) MWT1, (b) MSLT1, (c) MWT2, (d) MSLT2, (e) MWT3, (f) MSLT3, (g) MWT4, (h) MSLT4, (i) MWT5, (l) MSLT5. The sleep onset is represented in t=0 s with the vertical black line. The continuous line represents the averaging of the *FDAMIF_Re₃(β)* with respect to the time. The results of statistical analysis between EDS vs. WDS patients for each window are shown by black squares and black triangles that indicate the time instants in which p-value<0.05 and AUC>0.75, respectively.

Tables:

Table 1. Study 1: AMIF measures that have given the best performances differentiating the alert from the sleepy groups during the first minute of the tests, with the patient still awake.

VARIABLES	*EDS* (*m*±*SE*)	*WDS* (*m*±*SE*)	*p-value*	*Sen (%)*	*Spe (%)*	*AUC*
Study 1: MWT trials						
O1						
FDAMIF_Re$_3$*(β)*	0.7203±0.0110	0.7335±0.0092	0.0004	65	75	0.795
O2						
FDAMIF_Re$_3$*(β)*	0.7173±0.0112	0.7292±0.0090	0.0014	65	75	0.827
Study 1: MSLT trials						
C3						
FDAMIF_Re$_3$*(β)*	0.7071±0.0230	0.7326±0.0192	0.0007	75	75	0.815
C4						
FDAMIF_Sh(β)	0.8879±0.0092	0.8997±0.0034	<0.0001	65	100	0.915
mAMIF_Re$_{10}$*(β)*	0.1812±0.0195	0.1604±0.0082	0.0005	70	80	0.825
O1						
FDAMIF_Re$_3$*(β)*	0.7186±0.0138	0.7410±0.0093	<0.0001	80	90	0.898
O2						
FDAMIF_Re$_3$*(β)*	0.7154±0.0127	0.7410±0.0110	<0.0001	80	90	0.938

mean value (*m*) and standard error (*SE*)

Table 2. Individual analysis of MSLT and MWT trials: statistical analysis results between EDS and WDS group: *FDAMIF_Re3(β)* in channel O2.

Trial	*p-value (EDS vs. WDS)*	*Sen (%)*	*Spe (%)*	*AUC*
MWT1	0.0071	55	75	0.750
MSLT1	0.0004	80	80	0.830
MWT2	0.0439	60	60	0.687
MSLT2	<0.0001	85	95	0.922
MWT3	0.0018	70	85	0.790
MSLT3	0.0001	80	85	0.872
MWT4	0.0114	60	70	0.735
MSLT4	0.0018	60	75	0.790
MWT5	0.0531$^{n.s.}$	50	65	0.680
MSLT5	0.0001	60	100	0.890

n.s.: not significant.

Table 3. Study 1: CMIF measures that have given the best performances differentiating the alert from the sleepy groups during the first minute of the tests, with the patient still awake.

VARIABLES	*EDS* (*m*±*SE*)	*WDS* (*m*±*SE*)	*p-value*	*Sen (%)*	*Spe (%)*	*AUC*
Study 1: MSLT trials						
F4-C4						
maxLCMIF_Re$_{05}$*(θ)*	0.3823±0.0685	0.3003±0.0609	0.0004	80	70	0.828
F3-O2						

FDCMIF_Re10(β)	0.4982±0.1232	0.7110±0.2079	<0.0001	95	80	0.865
C4-O1						
mCMIF_Re100(β)	1.2993±0.0818	1.1993±0.0325	<0.0001	70	90	0.898
O1-O2						
mCMIF_Re50(β)	1.2695±0.0913	1.1683±0.0265	<0.0001	65	95	0.900

mean value (*m*) and standard error (*SE*)

Table 4. Study 2: multi-variable discriminant function between measures in MWT with their equivalent in MSLT; EDS vs. WDS Discrimination

	Sen (%)	*Spe (%)*	*AUC*
Study 2 AMIF			
O1			
FDAMIF_Re3(β)	80	90	0.903
O2			
FDAMIF_Re3(β)	75	90	0.935
Study 2 CMIF			
F3-O2			
FDCMIF_Re10(β)	90	80	0.863
C3-O2			
mCMIF_Re30(β)	70	100	0.928
C4-O1			
mCMIF_Re30(β)	70	95	0.905
C4-O2			
mCMIF_Re30(β)	80	100	0.938

AMIF and CMIF measures with p- value<0.05

Table 5. Traditional measures and discrimination of EDS vs. WDS in each of the Studies

Study	**TEST**	**Measures**	*EDS* (*m±SE*)	*WDS* (*m±SE*)	*p-value*	*Sen*(%)	*Spe*(%)	*AUC*
1								
		Channel F3						
	MWT5	P_θ	0.1719± 0.1029	0.1967 ±0.9100	0.0901	65	70	0.675
		Channels C3 -C4						
	MSLT5	*Cf SEF50* (β)	23.28 ± 0.37	24.72± 0.38	0.0127	60	60	0.731
1								
		Channel C3						
	MWT	*mF*(α)	10.64± 0.41	10.48± 0.35	0.0961	75	60	0.655
		Channels C4-F4						
	MWT	*Cf m*(θ)	0.559± 0.175	0.427 ± 0.158	0.0179	65	70	0.712
1								
		Channels O1						
	MSLT	*mF*(β)	21.84± 1.61	23.30± 1.66	0.0083	70	65	0.745
		Channels O2-F3						
	MSLT	*Cf SEF50*(*TB*)	20.93 ±4.66	25.84 ±5.44	0.0051	70	70	0.750
2								
		Channels O2						
	MWT-MSLT	*mF*(β)	21.72 ±1.57	23.00 ±1.65	0.019	80	70	0.747
		Channels F4-O2						
	MWT-MSLT	*Cf m* (δ)	0.623± 0.0893	0.499 ±0.162	0.0012	75	55	0.750
3								
		Channel F3						
	MWT3	P_θ	0.1753± 0.2035	0.1243 ±0.6743	0.0341	70	60	0.705
		Channels F3-F4						
	MWT3	*Cf m* (θ)	0.524± 0.277	0.457 ± 0.211	0.0312	70	60	0.695