Investigation of Sleepiness Induced by Insomnia Medication Treatment and Sleep Deprivation

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Abstract. The main objective of this work is the study of EEG signals in order to investigate sleepiness induced from drug administration for insomnia and sleep deprivation. Data used in this work were obtained from real experiments in FORENAP, France and in CERTH, Thessaloniki, Greece. The features under consideration are Power Spectrum in certain frequency areas, alpha slow-wave index (ASI) and Fractal Dimension (FD) for placebo and verum subjects. Studying these features in the above groups, we found that sleepiness due to hypnotic medication and due to sleep deprivation can cause different behaviour in brain activity at certain locations. These EEG characteristics could be used for the classification of the medication intake (verum or placebo) and its effect.

Keywords: insomnia, sleep deprivation, EEG signals.

1 Introduction

Insomnia is a medical disorder of sleep patterns characterized by difficulty in falling asleep, remaining asleep, or both. It affects millions of people and can be caused by many different conditions, diseases, and circumstances. Some effective insomnia treatments focus on changing the sleep behaviours and habits, while others require medications and supplements.

It is known that in humans sleep does not begin the same time in all cortical areas. Topographical and frequency changes observed in EEG data effect the wakefulness-sleep transition and allow us to describe the state of human brain before and after sleep on set [1].

Sleep deprivation is an overall lack of the necessary amount of sleep. Changes in brain activity have been observed during sustained wakefulness. Assessment of EEG power density in sleep deprived people [2] demonstrated an incensement in the 6.25-9.00 frequency range. Fluctuations in the energy of theta and alpha bands can be electrophysiological correlated to the "waking intensity" [3], [4]. Sleep-deprived subjects showed shifted patterns of brain activity, but research in this area is still controversial.

In this work we examine the coexistence of EEG topographical and frequency changes in order to elucidate differences in sleepiness due to hypnotic drug administration and due to sleep deprivation.

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2 Methods

In this analysis two datasets were used: a) dataset with drug induced sleepiness, b) dataset with sleepiness induced by sleep deprivation.

Concerning the first one, 14 male subjects aged from 18 to 40 years were selected as volunteers, in FORENAP. EEG data were collected after lorazepam 2.5 mg single administration in the morning to healthy people participated in the study. Lorazepam is a benzodiazepine drug with short to medium duration of action. It is known for its anxiolytic, amnesic, sedative/hypnotic, anticonvulsant and muscle relaxant properties by slowing down the central nervous system. As a psychoactive drug, it is useful in treating insomnia. For each subject two conditions were examined: verum and placebo, with recordings corresponding to different times during the day and night until next morning (recordings: t_1: one hour before drug intake, t_2: drug intake, t_3:one hour after drug intake, t_4:two hours after drug intake, t_5: three hours after drug intake, t_6:four hours after drug intake, t_7:five hours after drug intake, t_8:six hours after drug intake, t_9:eight hours after drug intake, t_{10}:ten hours after drug intake, t_{11}:twelve hours after drug intake, t_{12}:thirteen hours after drug intake). EEG signals were obtained with eyes closed during 3 minutes in resting condition. Standard channels used : chan.1 : FP1, chan.2 : FP2, chan.3 : F7, chan.4 : F3, chan.5 : FZ, chan.6 : F4, chan.7 : F8, chan.8 : T3, chan.9 : C3, chan.10 : CZ, chan.11 : C4, chan.12 : T4, chan.13 : T5, chan.14 : P3, chan.15 : PZ, chan.16 : P4, chan.17 : T6, chan.18 : O1, chan.19 : 0Z, chan.20 : O2.

For the pre-processing of the data, the average of all channels were calculated as reference and subtracted from all channels. Designated artifact regions were zeroed. Basic filtering was done at: 0.5-25 Hz. During the basic processing part, the standard 20 channels mentioned before have been used for analysis, not the extra ones.

The second dataset was obtained from an experiment [5] that took place at CERTH, Thessaloniki, Greece, from 6 June till 27 July 2005. Subjects participated in this one, were average drivers (mean driving experience: 8.3 years), with a mean 26.5 years and were asked to stay awake for at least 24 hours. The level of sleepiness was estimated by using the Karolinska Sleepiness Scale (KSS), [6] ranging from 1(very alert) to 9(very sleepy). The KSS test has been found to be related to EEG and behavioral variables, indicating a high validity in measuring sleepiness [7].

Data acquisition was performed for 20 minutes in a quite, dark environment. Recordings corresponding to the last 3 minutes were analyzed, in correlation with the data from the previous experiment. A sampling rate of 200Hz was used and the amplitude range was ± 20μV. Band bass filtering at the range of 0.5 to 70Hz was applied, with a notch filter ate the 50Hz power supply component.

During preprocessing [8], EEG data were Band pass filtered (3rd order Butterworth filter, Band pass range: 0.5 – 45 Hz) and artifacts were removed by Independent Component Analysis (ICA) technique. Finally, data were filtered to 0.5-25Hz, in order to have the same spectral range as the first dataset.

For the assessment of differences in brain activity between subjects manifesting sleepiness under insomnia medication (verum and placebo groups) and sleep deprived subjects with manifested sleepiness, spectrum analysis was applied. The extracted features were Power Spectrum in the frequency bands: delta (1-4Hz), theta (4-8Hz), alpha (8-13 Hz), beta (13-22 Hz) and ASI- alpha slow-wave index

(ASI=alpha/(delta+theta)) , related to arousal level. Fractal Dimension (FD) was also calculated for EEG signals, an indicatr of the system's complexity, related to both arousal/sleepiness and vigilance.

3 Results

Using the aforementioned features, the verum/placebo differences before medication were first assessed, forming the baseline for the drug effect. Then the differences between the two conditions were assessed again for the recordings one hour after medication intake, when drug effect is expected to be high. In parallel, these characteristics were compared with the ones of sleep- deprived subjects manifesting sleepiness.

Power spectral analysis revealed important differences between verum and placebo group in delta, alpha and beta frequency ranges for certain scalp locations.

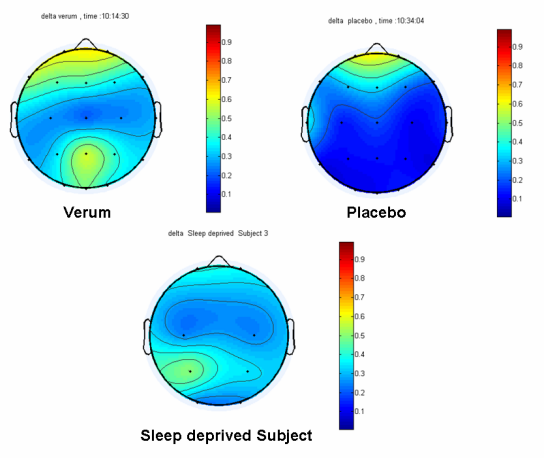

Fig. 1. Topographic map of a scalp data field with specified channel locations, show the brain activity for a subject for delta band, one hour after lorazepam administration and for a sleep deprived subject

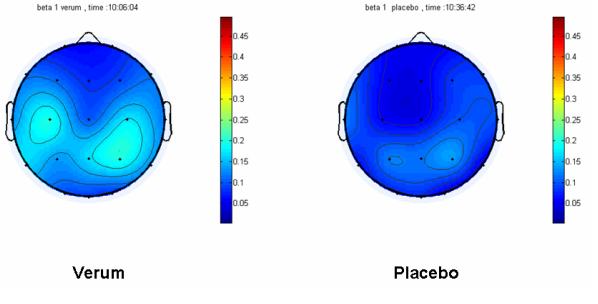

Fig. 2. Energy distribution for a verum and placebo subject one hour after drug intake at 13-22Hz

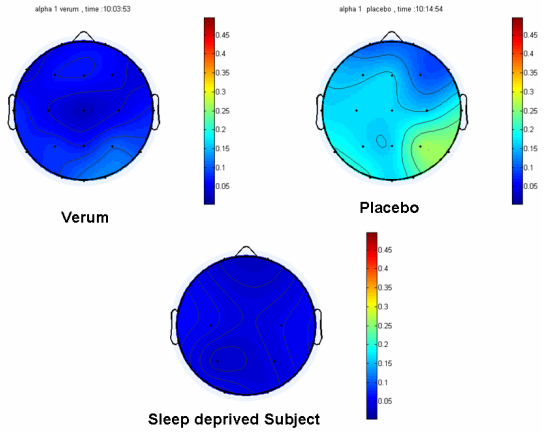

Fig. 3. Energy distribution for a verum and placebo subject one hour after drug intake and for a sleep deprived subject, for the alpha band

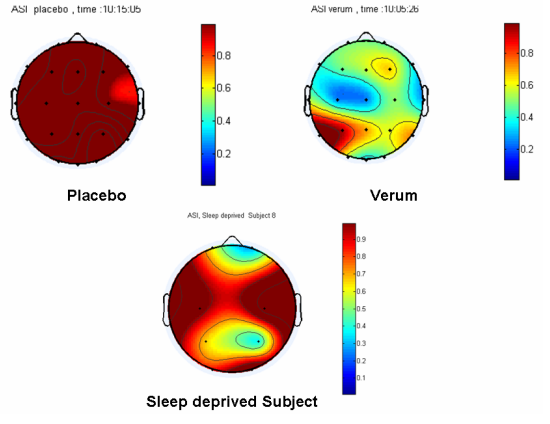

Fig. 4. Topographic map of a scalp data field with specified channel locations, show ASI one hour after lorazepam administration for a subject under verum - placebo conditions and for a sleep deprived subject

More specifically, for 1-4Hz frequency range and for the verum group, after drug intake, a predominance was observed for channels Fp1, F7, F3, Fz, P3, P4, and Pz. Placebo subjects showed lower energy values in comparison with verum and sleep deprived subjects. A topographic map of a scalp data field in a 2-D circular view shown in Fig.1, illustrates energy distribution at 1-4Hz, for a verum and a placebo subject one hour after drug administration and for a sleep deprived subject.

Energy increases for channels F3, C3, P3, P4, Cz, C4, T5 and T1 in beta (13-22 Hz) band for subjects that took lorazepam, one hour after the drug intake. Fig.2 shows an example with the energy distribution in the channels mentioned before for a verum and placebo subject, one hour after having 2.5 mg of lorazepam.

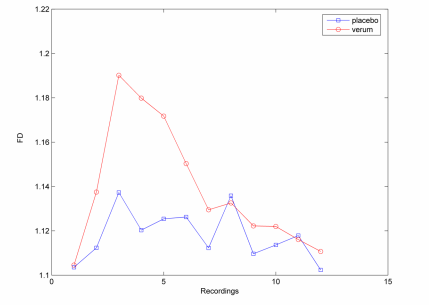

Fig. 5. Evolution of FD with time, for a specific subject and channel C3

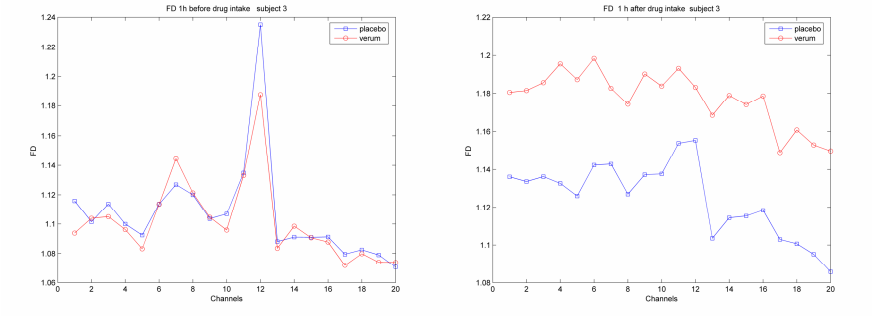

Fig. 6. FD for all channels, one hour before drug intake and FD for all channels, one hour after drug intake

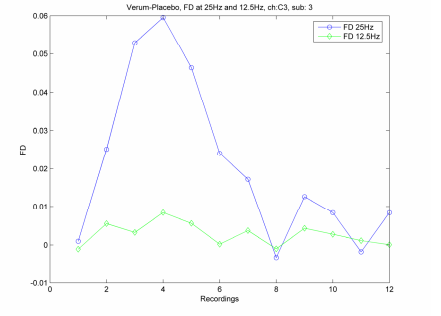

Fig. 7. FD difference between verum and placebo (FDv - FDp) for filtered signals at 25 Hz and 12.5 Hz for one subject

After one hour of drug administration, energy for alpha band (channels: F3, C3, Cz, C4, T5, T6) decreased for verum subjects, compared to placebo, and the alpha band levels where lower than in sleep-deprived subjects (Fig.3).

ASI feature indicating arousal decreases with verum in comparison not only with placebo, but also with sleep deprived group, since energy in delta and theta frequency

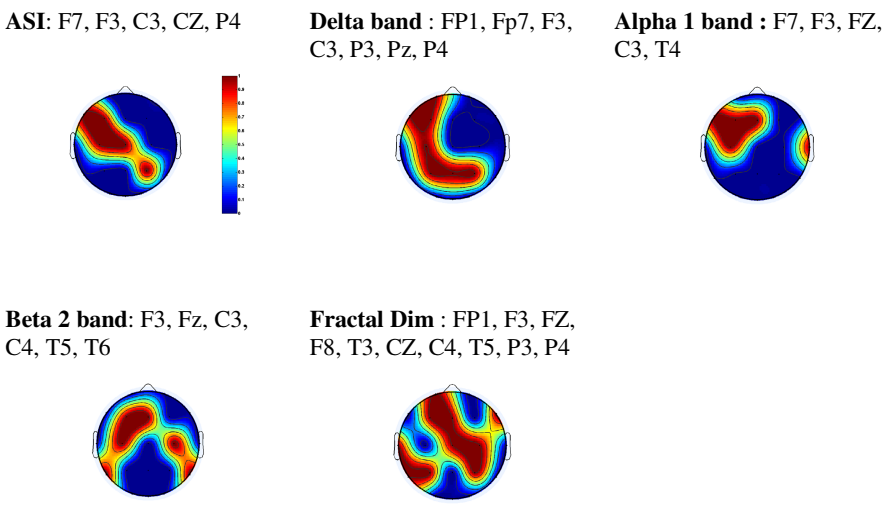

Fig. 8. Topographic map of a scalp data field with specified channel locations, show with red the positions that correspond to the statistically significant changes described above between verum and placebo, one hour after drug intake

bands for subjects under medication has higher values in comparison with sleep deprived subjects. An example can be seen in Fig.5.

EEG activity across delta/theta/sigma (12-15Hz) frequency range for channels FP1, FP2, F7, F3, Fz, F4, F8, C3, Cz, C4 was also significant different between verum and placebo groups, for all the EEG recordings.

Finally FD feature was calculated for subjects that took hypnotic drug and for placebo subjects. FD for verum group appeared significantly higher than in placebo group, while these differences dimish after 24 hrs. Fig.5 shows the FD evolution for C3 channel for a specific subject. In Fig.6 FD is plotted versus channels for the same subject, one hour before drug intake, while Fig.7 shows the situation one hour after drug intake, both for verum and placebo subjects. The difference between FD values for verum and placebo decreases by filtering the EEG signals, as shown in Fig.9 at 25 Hz and 12.5 Hz, indicating that the observed increased energy in beta band for verum could be partly responsible for the altered FD values in this group. However, more studies are needed, as fractal dimension is known to be affected by the EEG signal bandwidth. Furthermore, it is characteristic that on average the fractal dimension of the sleep deprived subjects who manifested sleepiness was also high, in comparison with the FD measured in the other subject group.

Overall, statistical differences were detected with the Wilcoxon rank sum test. Comparing the verum/placebo features before drug intake, statistical differences were not found in any EEG channel. On the other hand, one hour after drug intake, statistically significant changes were found between verum and placebo in ASI, Fractal Dimension, and bands Delta, Alpha1 ans Beta 2, as depicted in Fig.8 and Table. 1.

Table 1. P-values for Wilcoxon rank sum test results, corresponding to differences in EEG channel recordings as described above, between verum and placebo subjects, one hour after drug intake

	ASI	Delta	Alpha 1	Beta 2	FD
FP1		0.0409			0.0229
F3	0.0366	0.012	0.0229	0.0203	0.0409
F5			0.0409		
FZ				0.0291	0.0456
F8					0.0366
F7	0.0123		0.0409		
C3	0.0258	0.0203	0.0229	0.0456	
C4				0/0366	0.0456
CZ	0.0159				0.0291
P3		0.0229			0.014
P4	0.0326	0.0054			0.0336
PZ		0.0366			
T3					0.0291
T4			0.0159		
T5				0.0366	0.0203
T6				0.014	

4 Discussion

The analysis in this work demonstrates that power spectrum energy and ASI for certain EEG channels can be characteristics different for the three subject groups under consideration. Studying these features in the above groups, we found how sleepiness after drug intake is reflected in the EEG features, and moreover that sleepiness due to medication (one hour after drug intake) and due to sleep deprivation can cause different behaviour in brain activity at certain locations. Drug intake causes increase in delta/beta band and decrease in alpha band, as well as an increase of the fractal dimension in almost all channels.. Differences were not significant in the occipital channels, but rather in the left centro-parietal area. Furthermore, it is interesting to note that ASI index as well as fractal dimension was higher for the sleep deprived than medication group, suggesting that drowsiness or sleepiness due to medication is higher, or that the sleep-deprived group maintains more mental ability than the medication group. However, the fact that data for these two groups (medication and sleep deprivation) were produced from two distinct experiments consists a limitation to this study. Furthermore, extended experiments would be required to reveal to what extent these conditions cause a combination of sleepiness and hypovigilance, or preferably one of them.

Concluding, altered FD of EEG signals could support the detection of brain patterns in verum group, for the specific drug administration. Spectral characteristics discussed in this paper could also address the detection of drug administration effects, discriminating between verum and placebo, and also between medically and naturally induced sleepiness.

Acknowledgments

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