POLITECNICO DI TORINO

MASTER'S DEGREE IN BIOMEDICAL ENGINEERING

Computational approaches to the study of REM Sleep Behavior Disorder

Supervisors:
Prof. Gabriella Olmo
Ing. Irene Rechichi

Candidate:
Daniele Tarantini
Matr.: 279903

Academic year 2022/2023

Abstract

Parasomnias are disorders that afflict a part of the population. Often can be easily solved, others instead can lead to more serious disorders, such as REM behavior disorder (RBD) as it can be a warning premotor for neurogenerative diseases such as Parkinson and Dementia with Lewy bodies. The study carried out makes it possible to analyze the various stages of sleep and subsequently extract the features of each stage with EMG data obtained from the Sleep Medicine Center (CMS) database. The data, however, were noisy, so they were pre-processed with bandpass and notch filter because, due to the machines used, for each measurement it was noted there was a peak in 45 Hz, which was removed for all subjects. The distinction of the various stages of sleep was made by analyzing the hypnogram provided and, in particular, in the REM stage, REM sleep without Atonia (RSWA) scoring was calculated with the Montrèal and SINBAR method. The extracted and selected features of each stage were input to machine learning algorithms with the aim to automatically differentiate a patient from a healthy control subject. Supervised learning model (SVM) has been used and has been validated with cross-validation. Performance is relatively high with regards to identification of an RBD subject from a healthy one (85% of accuracy), however performance impairs when the RBD subject must be distinguished from a RSWA subject (73.68% of accuracy).

Furthermore, with the analysis of the phasic and tonic activity, the envelope of the tonic phase during REM sleep of the various subjects was studied, first by removing the phasic peaks and subsequently by enveloping the remaining tonic phase. It has been noted that in RBD subjects the envelope trend is periodically modulated, but the reason is yet to be understood. This can be a starting point for being able to compare the envelope trend of the other muscles to differentiate them or find common qualities.

Contents

List of Figures

List of Tables

Chapter 1

Healthy and unhealthy sleep

During a physiological sleep, the body condition is anabolic, in order to restore the nervous, immune, skeletal and muscular systems. In fact whole-organism metabolic rate during sleep is even lower than resting waking metabolic rate. There are many hypotheses that sleep's function is to reduce caloric use in order to regain energy used during wakefulness restoring its adenosine triphosphate (ATP) reserve, the molecule used for short-term storage and transport of energy; in this way the brain maintains memory and cognitive function. In other words, the brain uses actually less energy during sleep than it does when awake, especially during non-REM sleep [2, 3]. Furthermore, during sleep, the sensory threshold increases, which means that for the body to perceive a stimulus, it must be intense, like a loud noise.

1.1 Sleep stages

Sleep occurs in repeating stages, in which the body mainly alternates between REM sleep (REM) and non-REM sleep (NREM). The stages of sleep were first described in 1937 by Alfred Lee Loomis and his coworkers, but their name was "level" from A to E, representing the spectrum from wakefulness to deep sleep. Subsequently, in 1953, REM sleep was distinct from others, and then William Dement and Nathaniel Kleitman reclassified sleep into four NREM stages and REM. Officially the stages were standardized in 1968 by Allan Rechtschaffen and Anthony Kales in the famous "R&K sleep scoring manual", also known as "R&K standard" [4].

Lastly, in 2007, the new "AASM Manual for the Scoring of Sleep and Associated Events" has been published so it could be useful for a complete study of the polysomnography (PSG) because also arousal, respiratory and cardiac events were added. The following stages were officially proposed:

- Stage W (wakefulness)
- Stage N1 (NREM sleep)
- Stage N2 (NREM sleep)
- Stage N3 (NREM sleep)
- Stage R (REM sleep)

In general, during NREM sleep, the body temperature and heart rate fall [5], and the brain uses less energy. Instead, during REM sleep, that represents a small portion of total sleep, there are fast brain waves, eye movements, muscles are completely relaxed, and the subject can dream. For these reasons this stage of sleep occasionally is also called "paradoxical sleep" [6] because the awakening threshold is high, despite our brain is mighty active but but awakening in this phase allows the memory of what was dreaming. The sleep cycle of alternate NREM and REM sleep takes an average of 90 minutes, occurring 4–6 times in a good night's sleep [7].

1.1.1 Stage W

Wakefulness, through the reading of the electroencephalographic (EEG) signal, is characterized by the presence of alpha waves (from 8 to 13 Hz) [8] visible in the posterior regions of the head. The alpha rhythm is sometimes not clearly distinguishable, in fact about 10% to 20% of healthy people have little or no alpha rhythm. In these cases, wakefulness can be found and scored through electrooculohraphy (EOG), by observing the presence of one of three characteristics: eye blinks, eye movements and irregular conjugate eye movements with normal or high chin muscle tone. Lastly, submental electromyography (EMG) is relatively high tone because of the high-amplitude muscle contractions and movement artifacts.

1.1.2 NREM stages

N1 sleep stage

The N1 sleep stage is also referred to as transitional sleep; the alpha activity is often lost or less than 50%, and it is defined by the presence of low-amplitude, mixed-frequency activity, in particular it is scored when more than 15 seconds ($>$ 50%) of the epoch (30 s) is made of theta activity (4 to 7 Hz) [8]. Amplitudes of EEG activity are less than 50 to 75 μV. The EOG shows slow eye movements because the eyes begin to slowly roll and the submental EMG is lower in amplitude than in stage W. In fact, the EMG shows less activity than in wake stage, but the

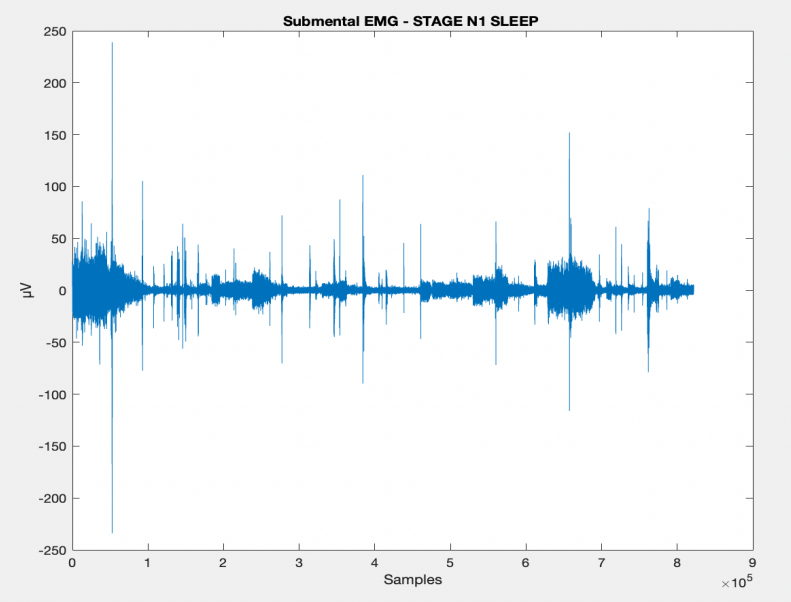

Figure 1.1: N1 sleep stage of a healthy subject from CMS database

transition is gradual. If an arousal occurs in this stage and if the burst results in alpha activity for greater than 50% of the record, the epoch is scored as stage W. An example of EMG is in Figure 1.1. Physiologically the subject's breathing gets slow, heart rate becomes regular, blood pressure falls and the subject shows little or no body movement, but the sleeper wakes up easily even with small external stimuli.

N2 sleep stage

The N2 sleep stage is also called spindle or intermediate sleep. It is an intermediate stage of sleep, but it represents up to 50% of PSG recording in adult patients. It is characterized by predominant theta activity (4 to 7 Hz EEG activity), occasional quick bursts of faster activity, but overall the EEG shows minimal alpha activity. Furthermore, the duration of delta activity is the threshold for differentiating state N3 from stage N2; indeed, if delta activity occurs for less than 20% of the epoch, the latter is scored as stage N2, otherwise it is scored as stage N3, also called slow wave sleep. In this stage, sleep spindles and K-complexes begin to occur. Spindles are trains of waves with a frequency of 12-16 Hz and lasting 0.5-1.5 seconds, which persist throughout the duration of non-REM sleep [9].

K-complexes are sharp, mono-phasic or poly-phasic slow waves, with a sharply negative (upward) deflection followed by a slower positive (downward) deflection and usually they can be distinguished from the rest of the background. K-

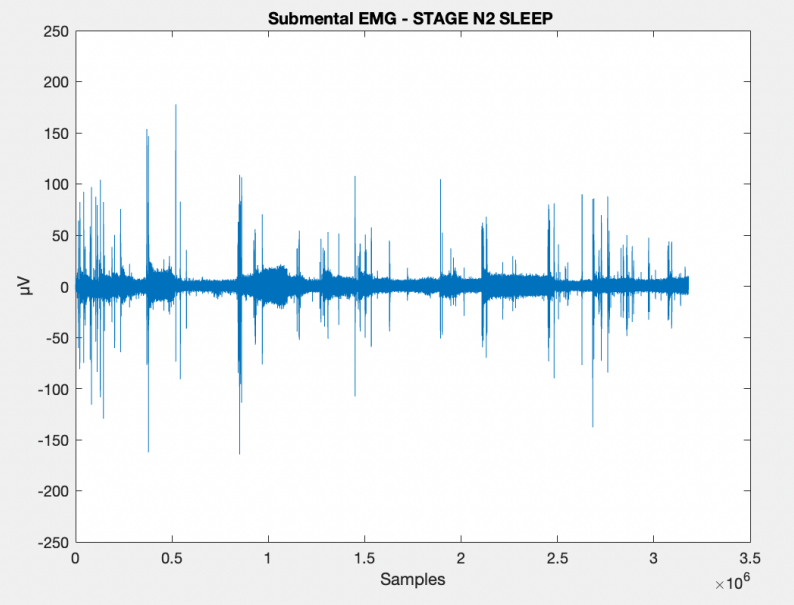

Figure 1.2: N2 sleep stage of a healthy subject from CMS database

complexes and sleep spindles are intermittent phenomena, they last at least 0.5 seconds, and may not always be present. However, their absence does not indicate that sleep has turned into the N1 stage, unless arousal occurs or there is a prominent body movement followed by slow eye movements. In general, the N2 stage sleep ends when there is a transition to W, N3 or R stages. Submental EMG activity is tonically low, and in figure 1.2 it is possible to see it.

In N2 stage sleep there is a decrease in physiological bodily functions, in fact blood pressure, cerebral metabolism, gastrointestinal secretions and cardiac activity decrease compared to stage N1. The subject descends deeper into sleep, becoming more detached from the outside.

N3 sleep stage

Stage N3 is the deepest stage of sleep, also referred to as deep sleep, delta sleep or, most commonly, Slow Wave Sleep (SWS). Previously this stage was divided into two sub-stages, but with the new AASM guidelines the two stages have been merged. It is scored when more than 20% of an epoch consists of slow wave activity, although K complexes and sleep spindles may persist in stage N3. SWS is characterized by low frequency bands (from 0.5 to 2 Hz) with high amplitudes (greater than 75 mV) [10]. In fact, it is properly incorrect to call it "delta sleep" because the frequencies are a subset of the delta wave band (from 0.5 to 4 Hz).

Physiologically a patient through SWS has the highest threshold for arousal

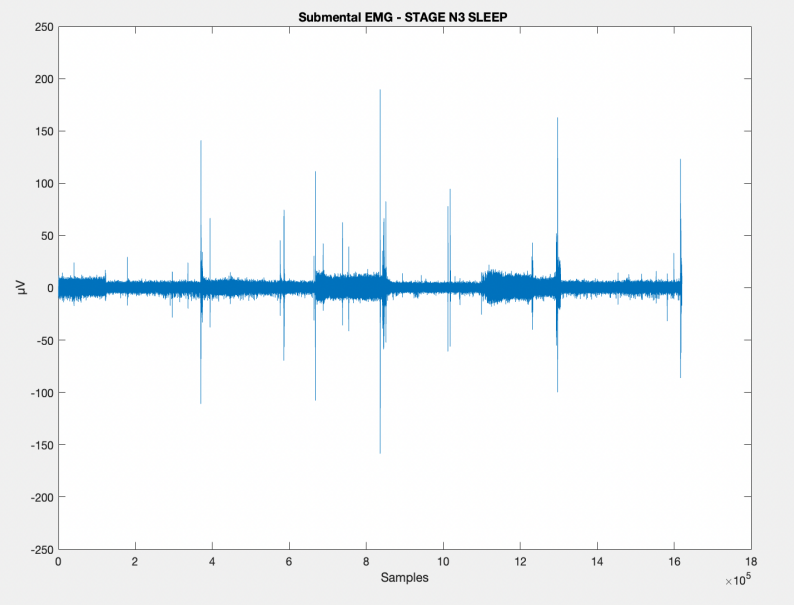

Figure 1.3: N3 sleep stage of a healthy subject from CMS database

because it is the deepest and restorative sleep type, and if the patient wakes up in this stage he may be confused and disoriented. For these reasons the muscle tone is even lower than in stage N1 or N2, as shown figure 1.3, and the eyes may stop moving.

R sleep stage

REM (o R) sleep stage is also called active sleep or paradoxical sleep because the human body results active at the brain level but there is muscle atonia. REM sleep typically occurs about 90 to 120 minutes after sleep onset in adults and it begins with a brief period but progressively the periods become longer during the night and it occupies 20% to 25% of the period of sleep. In R stage the human body increases physiological activity; blood pressure and pulse rate may increase or may show intermittent fluctuations, breathing becomes irregular and brain oxygen consumption increases. If patients wake up in this stage of sleep, they often can remember the dream, but if the patients have disorders associated with REM sleep they may not remember it and especially it could lead to a pathological situation, including different types of parasomnias, like REM sleep behavior disorder or REM nightmares.

The EEG shows low-amplitude, mixed-frequency EEG theta waves and some subjects also have prominent alpha frequencies, often 1 to 2 Hz slower than their alpha rhythm when they are awake. Instead, the EOG shows rapid eye movements

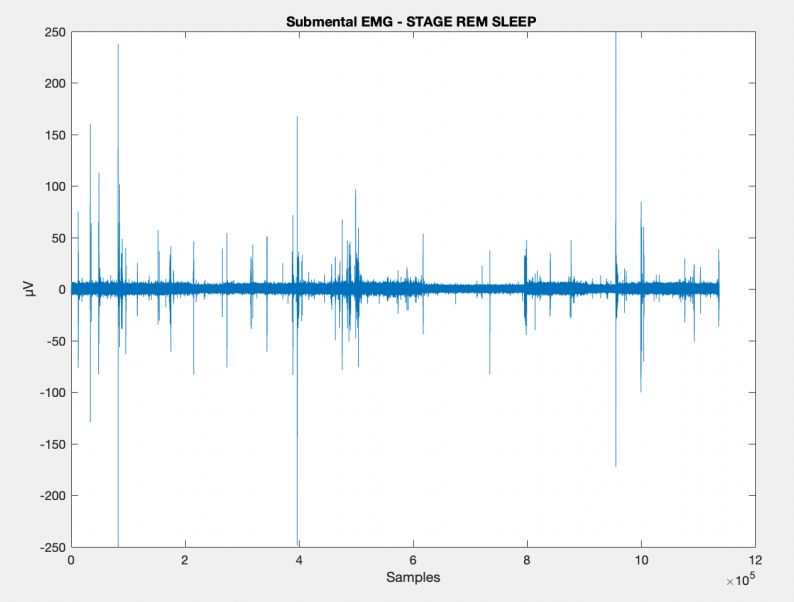

Figure 1.4: R sleep stage of a healthy subject from CMS database

(REMs) that are defined as conjugate (both eyes), irregular, sharply peaked eye movements with the duration of the initial deflection usually less than 500 ms.

The most important features for stage R are in the EMG. The submental EMG tone is at the lowest level of the whole PSG and there are particular waves as saw tooth waves and burst of EMG activity lasting <0.25 seconds overlapped on low tone background (Figure 1.4). It is possible to observe it well in the chin and anterior tibialis. In few words, stage R is scored if chin EMG tone is low and K complexes and sleep spindles are absent, even if the rapid eye movements have not yet started. A review of brain waves during stages sleep is shown in Figure 1.5.

1.2 Sleep Disorders

1.2.1 Guidelines

The main international classification of sleep disorders is the International Classification of Sleep Disorders (ICSD), first version published in 1990. It was developed as a diagnostic, epidemiological and clinical resource for sleep medicine researchers [11]. The first and subsequent versions were produced by the American Academy of Sleep Medicine (AASM) in collaboration with the American Sleep Disorders Association (ASDA), the European Sleep Research Society, the Japanese Society of Sleep Research and the Latin American Sleep Society, the main international

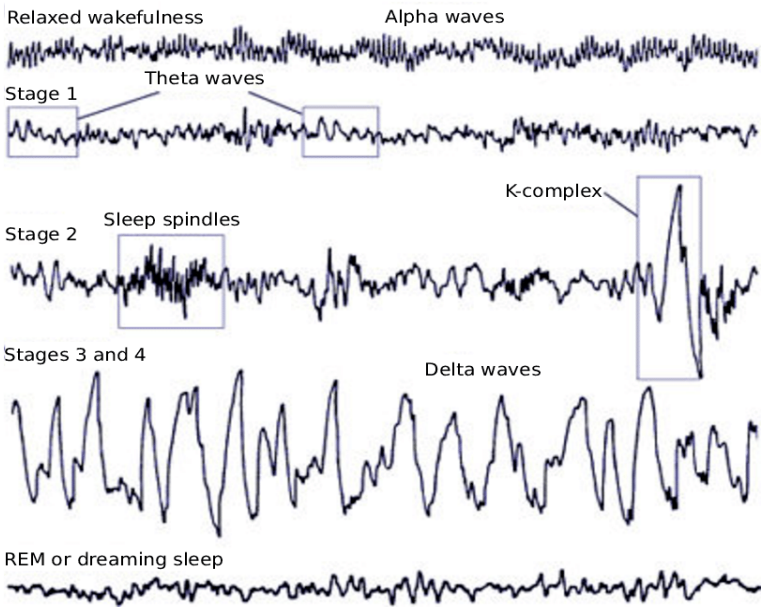

Figure 1.5: Brain waves during sleep stages [1]

sleep societies. A second edition was published in 2005 and called ICSD-2, but the third and current edition is about 2014 and it is called ICSD-3, also released by the AASM. The ICSD-3 lists the 83 disorders divided into 7 main categories [12]:

1. Insomnia
2. Sleep-related breathing disorders
3. Central disorders of hypersomnolence
4. Circadian rhythm sleep-wake disorders
5. Parasomnias
6. Sleep-related movement disorders
7. Other sleep disorders

1.2.2 Parasomnias

Parasomnias are defined as undesirable and abnormal behaviors, movements, emotions and dreams that occur predominately or exclusively during the sleep period. The main concept to understanding them is that the state of sleep and wakefulness are not mutually exclusive states, hence the severals variables that determinate the

states of wakefulness, non-REM (NREM) sleep and REM sleep may occur simultaneously or oscillate quickly. The parasomnias are classified according to ICSD-3 into the 3 categories [13, 14]:

- REM parasomnia, which includes nightmares and recurrent isolated sleep paralysis, but the most common and best studied one is REM sleep behavior disorder. The latter is the disorder that will be better explored later in this study.
- NREM parasomnia, which includes disorders such as the so-called sleepwalking, sleepterrors and confusional arousals. The treatment is often not necessary, but in rare cases the administration of drugs such as antidepressants and benzodiazepines is possible.
- Other parasomnias, those that do not fall into the previous two categories, such as exploding head syndrome, sleep-related hallucinations and sleep enuresis

1.3 RBD: REM Behavior Disorder

REM sleep behavior disorder (RBD) is a parasomnia characterized by repeated episodes of dream enactment with a partial or complete loss of normal skeletal muscle atonia during REM sleep, termed REM sleep without atonia (RSWA). The dream enactment behaviours exhibit an excessive motor activity ranging from simple twitches to strong ones, that may result danger for the patient and for sleeping partner, typically include kicking and hitting with screaming, shouting or laughing, even if speech is often incomprehensible. The behavior is linked to typical RBD dream contents because the patient tells of being chased, attacked or defending their partner from attack. RBD is common in patients affected by neurodegenerative diseases, belonging to the group of alpha-synucleinopathies, like Parkinson's Disease (PD), Dementia with Lewy bodies (DLB) and Multiple System Atrophy (MSA). RBD may be idiopathic (iRBD) therefore without known cause or symptomatic, caused by neurodegenerative disorders previously mentioned. In particular, it occurs more likely in patients with MSA (90–100% of cases), then DLB (70–80%) and finally in PD (25–58% of cases) [15].

1.3.1 Diagnosis of RBD

According to ICSD-3, the diagnosis requires PSG because it uses a combination of EMG and EEG to find the features of RSWA and to observe abnormal behaviors during REM sleep which are usually documented from a video recording during

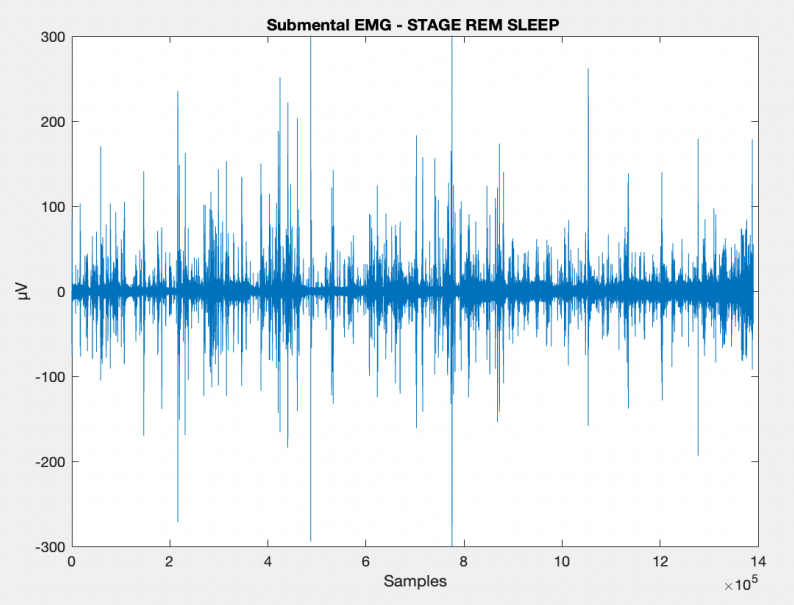

Figure 1.6: R sleep stage of a RBD patient from CMS database

the PSG or informally from the bed partner. Going into detail, RSWA consists of lasting loss over time of normal muscle atonia during REM sleep (i.e. tonic activity) and/or intermittent (i.e. phasic activity) excessive EMG activity during REM sleep, as shown in Figure 1.6. It is evident that the quantification of RSWA is critical in order to diagnose RBD, therefore several methods have been developed to evaluate motor activity during REM sleep.

Diagnostic criteria according to the International Classification of Sleep Disorders mainly include [16]:

- Abnormal and injurious REM sleep behaviors during PSG;
- Presence of RSWA on PSG;
- Sleep disorder is not better explained by another disorder.

The importance of only the RSWA, without any abnormal behavioral component, is uncertain, although there is some evidence that it can be a precursor to RBD, a kind of prodromal form of RBD.

1.4 Hypnogram

A graphic representation of sleep-stage sequence across the night is provided by hypnogram, a useful method to evaluate sleep continuity and to analyze the sleep

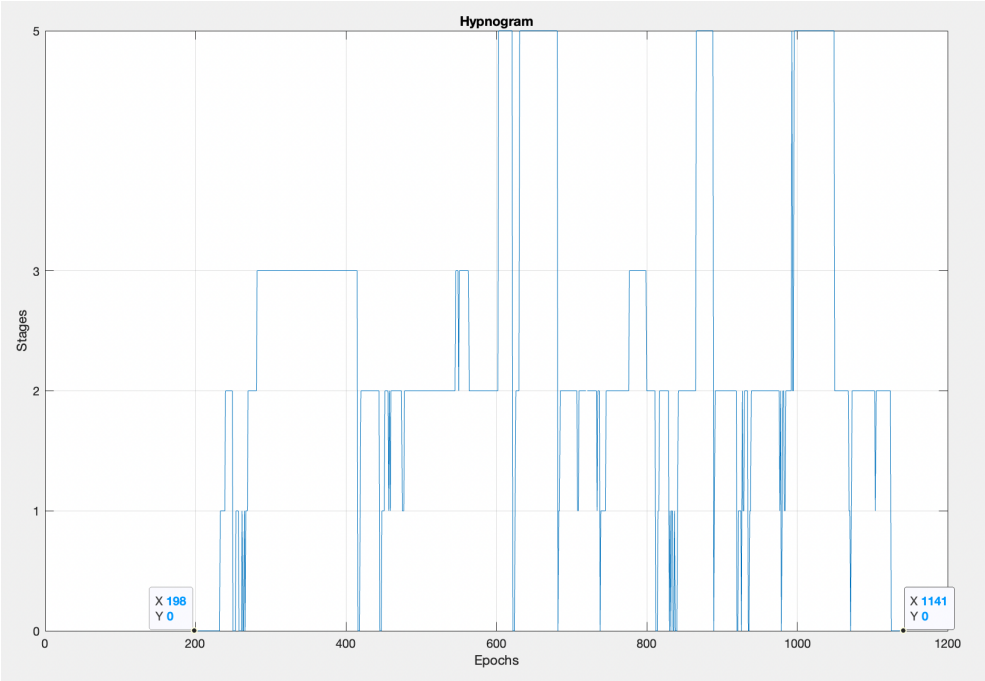

Figure 1.7: Hypnogram of a healthy subject from CMS database

cycle. Several parameters are usually computed from the hypnogram, such as the sleep efficiency (SE), sleep onset latency (SOL), REM sleep percentage, NREM sleep percentage and REM latency. These are just some of the parameters taken into consideration for the subsequent study of feature extraction, further explored in the Machine Learning chapter. In few words, the hypnogram provides a qualitative description of the sleep structure, and quantitative measures are drawn from it. The stage scoring is done on 30s epochs and therefore the polysomnographic recordings observed are divided into time segments.

In an average night of sleep of about 8 hours of a healthy subject, as can be seen in Figure 1.7, deep sleep N3 (stage 3) occurs mostly in the first part of sleep and awakenings (stage 0) are sporadic and short-lived. Another parameter to note visually is in the second half of the night's sleep, where the lengths of the REM sleep segments (stage 5) are longer than those in the first half of the night; this means that REM sleep lasts longer in the nocturnal sleep cycles near the end of the night. Awakenings immediately after the REM stage are good awakenings, instead those that occur in one of the other stages could be abrupt awakenings especially if they occur in the deep stages of sleep, as N2 and N3 stages.

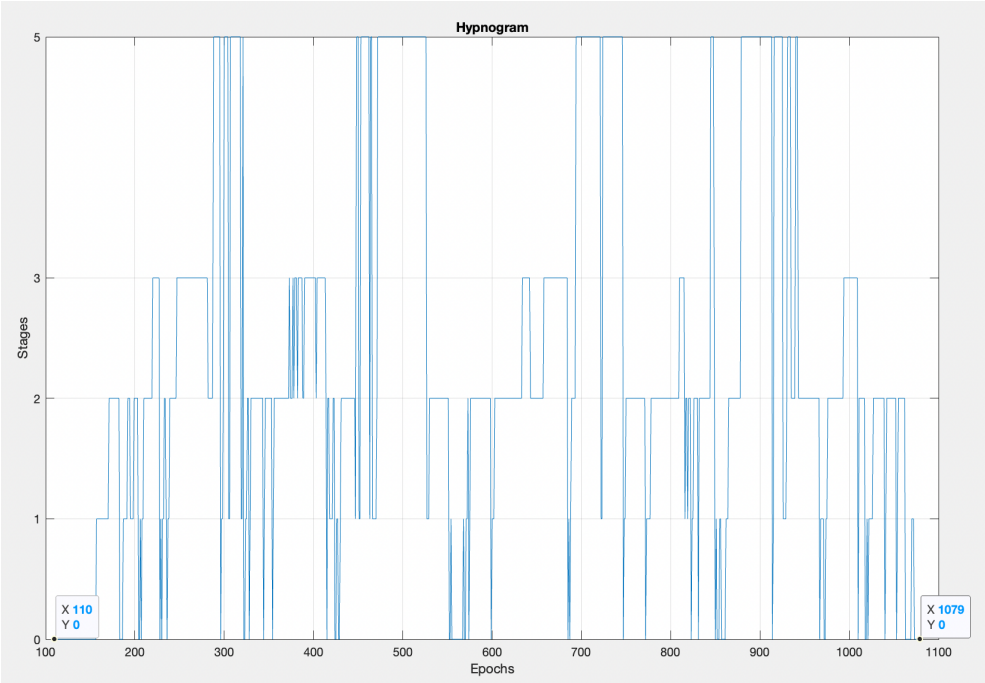

Figure 1.8: Hypnogram of a RBD subject from CMS database

1.4.1 Comparison

It is interesting to compare the various hypnograms to better understand how they change according to the subject's disease. In particular, this section compares the hypnogram of a RSWA subject (Figure 1.9) and a RBD subject (Figure 1.8) with a healthy subject (Figure 1.7). As regards the recordings, the waking state (stage 0) begins and ends at different times in the three subjects; in fact in the healthy subject it begins and ends in the epochs 198 and 1141, while in the subjects RBD and RSWA they begin respectively in the epochs 110 and 0, and end in epochs 1179 and 1198, but it varies from subject to subject.

As regards the stages, in unhealthy subjects it is not possible to define a sequence of stages of sleep because, as can be notice, the duration of each segment is short and changes suddenly. Furthermore, in the RBD subject the length of the REM segments is not progressive as in healthy subjects, but it is random, as is also the frequency of stage N3. Finally, as could be expected, the RSWA subject has particularly little stability in the REM stage, in fact many stage changes of very short duration are noted.

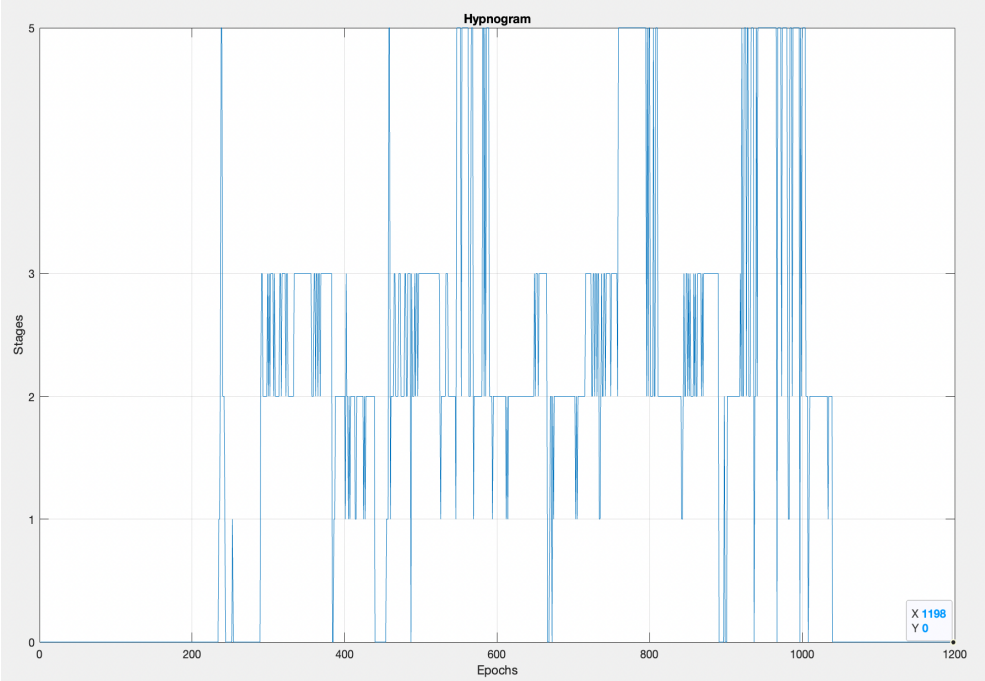

Figure 1.9: Hypnogram of a RSWA subject from CMS database

Chapter 2

Materials and methods

2.1 The goal of the study

The main goal of this study is to use machine learning to be able to automatically differentiate a healthy subject from a unhealthy one (RBD or RSWA) directly from the submental EMG signal. The submental EMG signal was recorded during a PSG, where other EMG, EEG and EOG signals were also recorded. In particular, the study can be divided into several steps:

1. Collection, selection and analysis of data from Sleep Medicine Center database;
2. Pre-Processing: filtering of noisy data, with particular attention to visible peaks in the PSD;
3. Scoring methods: implementation of algorithms capable of scoring the tonic and phasic activities of the submental muscle with the SINBAR and Montreal method;
4. Signal envelope: the envelope of the EMG signal of the tonic activity, useful for understanding whether there is a typical morphology of the tonic envelope;
5. Machine Learning: feature extraction and selection and implementation of a learning model to able to classify healthy and unhealty patients;
6. Results: cross-validation and accuracy.

2.2 Database

The sleep database was provided by the Sleep Medicine Center (CMS) at the Hospital "Molinette - Città della Salute e della Scienza di Torino", Turin, Italy.

It is a collection of 29 polysomnographies labeled as healthy, RBD, RSWA data. Data from OSAS patients were also provided but were not used for the purpose of this study. Summarizing the subjects studied in this work:

- 10 healthy subjects
- 10 RBD subjects
- 9 RSWA subjects

Each polysomnogram has two types of files: edf and txt extensions. The header of edf files is read by *"edfreadUntilDone"* function, and includes two outputs: the record of all signals and a data structure that contains information about instrumentation and measurement data. The latter includes patient and recording identification, information about the recording as the start date and start time, the number of data records and the number of signals in each data record. In this database each data record has 24 different signals from EMG at submentalis muscle, EEG, ECG, body temperature, heart rate, respiration signals as airflow, abdominal and thoracic displacements and oxygen saturation. Finally, the sampling frequencies and the unit of measure are present. For this study the sampling frequency is 256 Hz for all EMG of the submentalis muscle record. The unit of measure used is "μV" and if it is another unit it is changed in "μV".

The txt files contain polysomnography annotations to make hypnogram. The hypnogram was made through the function *"readscoreTurin"* and following AASM rules it was divided into 30-second epochs so that the hypnogram could be made and displayed. However, the goal was to display only the REM signal and this was possible by resampling the hypnogram on all signal samples because the signal taken was recorded in samples and subsequently stage 5 (REM) was taken from the last hypnogram made. Epochs or samples were removed as appropriate to match the number of 30-second epochs and signal length. This procedure allowed to visualize only the REM signal of the submental muscle as a function of all the samples recorded during the night, as shown in the Figure 1.4. The following data processing and the algorithm software implementation were performed in MATLAB R2021b language.

2.3 Pre-Processing

The signals of interest were noisy, in particular all of them exhibited a significant peak in 45 Hz due to the shifted powerline frequency. To understand which filters to implement, the power spectrum of each signal was calculated and displayed. Welch's PSD is estimated on the signal, from which, however, the average has been removed to remove any trends. The Hamming window over the entire length

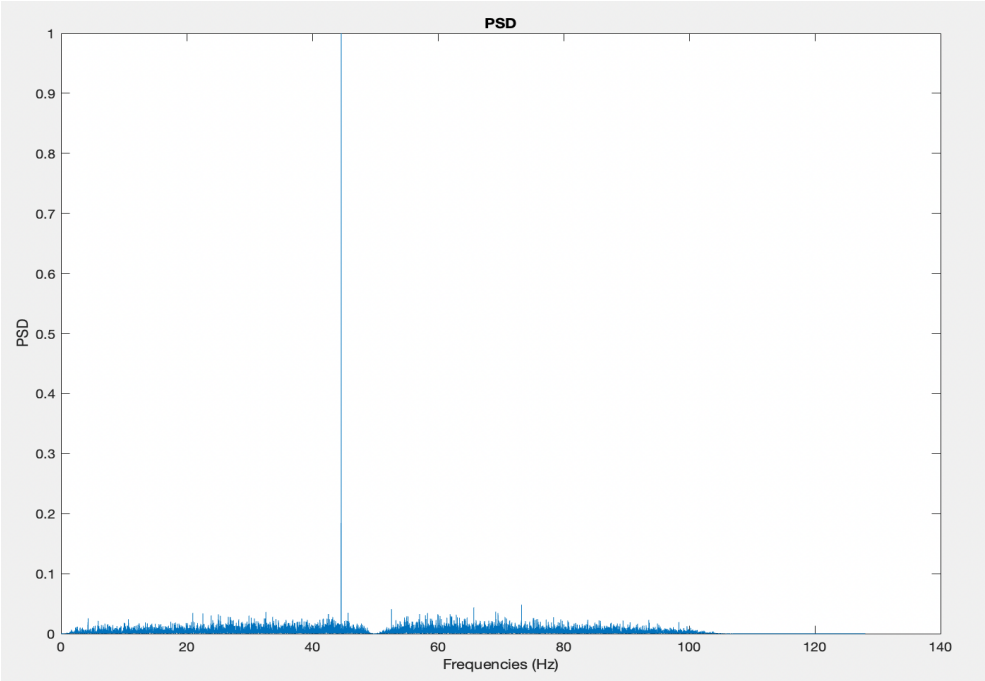

Figure 2.1: PSD of a submental EMG signal during REM stage of a healthy subject from CMS database

of the signal has been chosen as the window and as regards overlapping, the number of overlapping samples is equal to 50% of the length of the window. The number of discrete Fourier transform (DFT) points to use in the PSD estimate is 32786 points. An example of the results is shown in Figure 2.1, the PSD is normalized to its maximum, so it is between 0 and 1 in order to simplify the comparison with the other PSD.

2.3.1 Bandpass filter

The power spectral density is useful to deduce that the main information of the power density of the signal is between 10 and 100 Hz; in fact before 10 Hz the information is low and unstable, after 100 Hz it quickly tends to 0 Hz. For these reasons it has been decided to use a 10-100 Hz band pass filter. It is designed through a digital Butterworth filter with an order and a cutoff frequency determined by the MATLAB function *"buttord"* that is set so that guarantees no more than 4.5 dB of passband ripple and at least 20 dB of attenuation in the stopband.

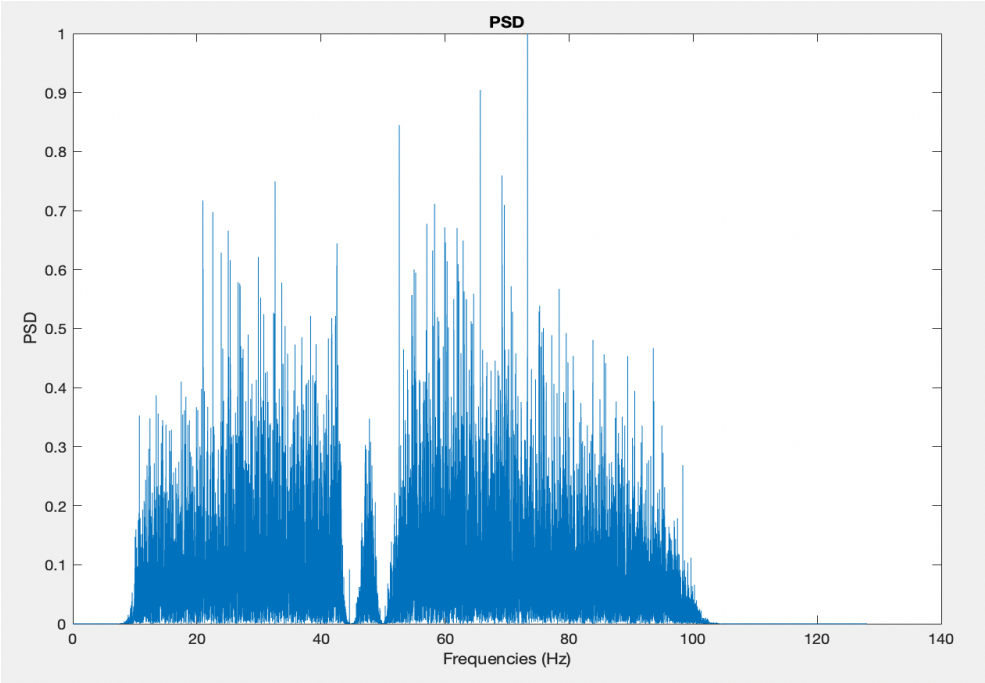

Figure 2.2: PSD of a filtered submental EMG signal during REM stage of a healthy subject from CMS database

2.3.2 Notch filter

The notch filter was used to limit the peak of the signal that can be seen in the PSD in the Figure 2.1 at powerline frequency of 45 Hz. The filter was then set with that cutoff frequency and a digital recursive filter was designed using the MATLAB function *"Yulewalk"*. It returns the transfer function coefficients of an n-order IIR filter whose amplitude-frequency response approximately corresponds to the input ideal values f and m, chosen with reference to an ideal notch filter. To choose the most suitable n-order, a loop repeated 100 times was implemented for which at each cycle the filter mask was displayed and superimposed to the previous ones. In this way the best frequency response was chosen that was able to filter better at the cutoff frequency without attenuating too much the adjacent frequencies.

Finally, to filter the signal with the coefficients obtained, the "filtfilt" function is used since the IIR filter has a non-linear phase response and therefore there is a phase distortion. The function performs zero-phase digital filtering by processing the data in the forward and reverse directions. The final result of the filtering of the previously signal is clearly observable in the Figure 2.2.

2.4 Scoring methods

Scoring RSWA is essential to help the diagnosis of RBD, and, as previously mentioned, it consists of sustained loss of the tonic activity due to the loss of normal muscle atonia during REM sleep and/or a considerable phasic activity due to excessive EMG activity during REM sleep. Therefore, it is essential to quantify RSWA with numbers and values in order to possibly be able to correctly diagnose RBD. The first visual scoring method for quantifying tonic and phasic chin EMG activities was originally developed in 1992 by Lapierre and Montplaisir, it is the so-called Montréal method [17]. It has been useful to study idiopathic RBD (iRBD) and RBD associated with neurodegenerative diseases, but it was never measured in a large group of RBD patients and normal controls until the year 2010, when the method was validated in a study managed by Montplaisir himself.

Another visual scoring method was performed by the Barcelona and Innsbruck groups, known as SINBAR group. The group performed an EMG analysis for the purpose of comparing RSWA assessed in 13 different body muscles and in different combinations to find the highest rates phasic EMG activity. Highest rates of phasic EMG activity were found in the mentalis muscle, the flexor digitorum superficialis (FDS) muscle in the upper limb muscles and the extensor digitorum brevis (EDB) muscle in the lower limb muscles, it was called the SINBAR montage [18]. Using this combination of muscles, EMG activity was present in 95% of all motor manifestations, more than two and a half times compared to using only the mentalis muscle in fact EMG activity was only present in 35% of behaviors.

2.4.1 Montréal method

The method is used to calculate Tonic density and Phasic density of the submental muscle. It is based on 30-second epochs and each epoch is analyzed and categorized as tonic or atonic and phasic or aphasic. Tonic and Phasic density, instead, is not calculated for each epoch but it is calculated on the whole signal because it represents the percentage of 30-second epoch scored as tonic or phasic respectively. The threshold tonic/phasic is defined as 40th percentile of the SWS sleep stage, namely background activity.

The function implemented on MATLAB is called *"montreal_tonic_phasic"* and has 3 input:

- FS: sampling frequency
- BKG: background activity of EMG muscle tone
- SIGNAL: filtered REM signal

And the output are clearly two: Tonic and Phasic density.

Tonic Density

The steps of the algorithm implemented to calculate Tonic Density are the following:

1. Signal rectification: all negative voltages are made positive, reversed with respect to the base line. It allows to have many benefits: a better reading of the signal and a more precise evaluation of the exceeding of the threshold, definitive later;
2. Signal is divided into 30-second epochs;
3. Threshold definition: the amplitude of a sample must be at least twice as large as the BKG activity or must be greater than 10 μV. Exceeding the threshold defines that sample's activity as *increased activity*;
4. Tonic activity definition: if more than 50% of the epoch samples exceed the threshold, the epoch is defined as *tonic*;
5. Tonic density is calculated as the percentage of tonic epochs out of total REM epochs.

REM sleep chin EMG activity was scored abnormal when tonic chin EMG density was $\geq 30\%$. [19]

Phasic Density

The steps of the algorithm implemented to calculate Phasic Density are the following:

1. Signal rectification;
2. Signal is divided into 30-second epochs;
3. Each 30-second epoch is divided in 2-second mini-epochs;
4. Threshold definition: the amplitude of a sample must exceed at least four times the amplitude of BKG activity to be considered *supra-threshold*. One or more consecutive supra-threshold samples are termed as a single *burst*.
5. 10 or more consecutive sub-threshold samples are considered to belong to two different *bursts*;
6. Phasic activity definition: if the bursts into the epoch have duration between 0.1 and 10 seconds, then the epoch is scored as phasic;

7. Phasic density is calculated as the percentage of the number of phasic epochs out of total REM epochs.

Phasic density of chin EMG was considered abnormal when it was $\geq 15\%$. [19]

2.4.2 SINBAR method

As previously described, the SINBAR group found the muscles with the highest rates of phasic EMG activity, i.e. mentalis muscle (submental muscle), flexor digitorum superficialis (FDS) muscle and the extensor digitorum brevis (EDB) muscle. In this study the tonic and phasic density are calculated only for the submental muscle also with the SINBAR method. The function implemented on MATLAB to calculate tonic and phasic density are called *"sinbar_tonic"* and *"sinbar_phasic"* respectively, and have 3 input as "montreal_tonic_phasic": FS, BKG and the filtered signal (submentalis EMG). The output is the Tonic Density in percentage.

Tonic Density

The steps of the algorithm implemented to calculate Tonic Density are the same of the Montréal method, in fact the result match each other. For the completeness of the study, the steps have been reported anyway in the following list:

1. Signal rectification: all negative voltages of the filtered signal are made positive;
2. Signal is divided into 30-second epochs;
3. The amplitude of a sample must be at least greater of two times than the BKG activity or must be greater than 10 μV. Sample activity is termed as *increased activity* when it exceeds at least one of the two thresholds;
4. The epoch is defined as *tonic* if more than 50% of the same epoch samples exceed the threshold;
5. Tonic density percentage is calculated as the percentage of tonic epochs out of total REM epochs.

The threshold score percentages for defining abnormal tonic density are the same of the Montréal method, hence when tonic chin EMG density is $\geq 30\%$. [19]

Phasic Density

The steps made of the algorithm implemented to calculate Phasic Density with SINBAR method are the following:

1. Signal rectification;
2. Signal is divided into 30-second epochs;
3. Each 30-second epoch is divided in 3-second mini-epochs, so as to form 10 mini-epochs for each epoch;
4. Threshold definition: the amplitude of a sample must exceed at least two times the amplitude of BKG activity to be considered *supra-threshold*. One or more consecutive supra-threshold samples are termed as a single *burst*.
5. 10 or more consecutive sub-threshold samples are considered to belong to two different *bursts*;
6. Phasic activity definition: if the bursts into the epoch have duration between 0.1 and 5 seconds, then the epoch is scored as phasic. Bursts outside the range were not counted because are not defined as phasic;
7. Phasic density is calculated as the percentage of the number of phasic epochs out of total REM epochs.

The percentage cut-off value of 3-second mini-epochs with phasic chin EMG activity is 16.3% [19]. If the phasic density exceeds this percentage, it is defined as unhealthy.

2.5 Envelope analysis

Envelope analysis of EMG in RBD patients was made because it could contribute to assist RBD diagnosis [20]. The envelope of EMG in this section focused in particular on tonic activity of healthy subjects and RBD patients during REM stage recorded during the PSG. The goal of the tonic activity envelope graph of an RBD patient is to find characteristics about the envelope morphology in order to be compared with the envelope morphology of a healthy subject or, more in general, to compare different envelopes of different muscles and understand if the trends are similar in order to facilitate the most correct diagnosis and, perhaps, even find a faster diagnosis directly from the envelope of the tonic activity of the muscle being examined.

To isolate tonic from phasic activity, the larger phasic bursts have been eliminated in order to flatten the graph and make it as tonic as possible. The algorithm

was implemented by dividing the REM sleep EMG signal into 60-second epochs and for each epoch the local maxima (peaks), the locations and the width of each were found using the MATLAB function *"findpeaks"*. The maximum peak width in seconds to define whether the samples belong to the same peak is 2 seconds because it is the most useful to characterize the signal trend. To eliminate the peak, the position and width were used in order to identify the signal segment to be deleted. Finally, the envelopes were plotted.

2.6 Machine Learning model

In this section, Artificial Intelligence (AI) is used to develop a Machine Learning (ML) model of the data extracted and processed in order to be able to classify in an automatic way. It must distinguish whether a subject is unhealthy or healthy by analyzing the filtered EMG signal of REM sleep. The steps for the development of the Machine Learning model are done as follows:

1. Feature extraction
2. Model training
3. Accuracy assessment

2.6.1 Feature extraction

The literature describes several features, but for this study only some of those proposed have been chosen, those deriving from the analysis of the EMG signal and the hypnogram, namely polysomnographic features. In total are extracted 49 features from the hypnogram and EMG signal and are divided in three different categories: polysomnographic, muscular (EMG) in the frequency domain and muscular (EMG) in the time domain.

The features computed on the hypnogram include the total hours of sleep (TST), lights-off to lights-on interval in hours (TIB), ratio between TST and TIB, proportion of N1, N2, N3 and REM sleep in TST and the average length of N1, N2, N3 and REM segments. The features that represent information in the frequency domain include the spectral edge frequency at 95% of REM signal (SEF95) that indicates the highest frequency below which 95% of the REM signal power is located and in the same way the spectral edge frequencies were calculated at different percentages such as 25% (SEF25), 50% (SEF50) and 75% (SEF75) [21, 22]. Finally, the main features computed in the time domain are background activity evaluation of muscle, tonic and phasic density, number of peaks and peaks width. All features have been normalized between 0 and 1. The details of features computed are defined in detail in Table 2.1.

Type	Name and description
PSG	**Sleep Onset Latency (SOL)**: the amount of time required to fall asleep (minutes) **Total Sleep Time (TST)**: total hours of sleep **Time in Bed (TIB)**: lights-off to lights-on interval (hours) **Sleep Efficiency (SE)**: the ratio between TST and TIB (%) **Minutes of REM Sleep (MREM)**: total duration of REM Sleep (minutes) **Average Length N1 (ALN1)**: average length of N1 segments (minutes) **Average Length N2 (ALN2)**: average length of N2 segments (minutes) **Average Length SWS (ALN3)**: average length of SWS segments (minutes) **Average Length REM (ALN5)**: average length of REM segments (minutes) **Proportion of N1 Sleep (PN1)**: N1 sleep in TST (%) **Proportion of N2 Sleep (PN2)**: N2 sleep in TST (%) **Proportion of SWS Sleep (PN3)**: SWS sleep in TST (%) **Proportion of REM Sleep (PNR)**: REM sleep in TST (%) **Waking proportion (WP)**: awake time during the night (%) **Wake After Sleep Onset (WASO)**: the amount of time the subject is awake during the recording (minutes)
EMG (TD)	**Statistical measures**: mean, standard deviation, skewness, kurtosis, max, min **Energy**: for every 30 s epoch the mean rectified amplitude is calculated **Background activity (BKG)**: the 40th percentile of the SWS sleep stage (μV) **Tonic/Phasic Density**: for every 30 s epoch tonic/phasic density is calculated using SINBAR method (%) **Envelope**: number of peaks, peak amplitude, peak width
EMG (FD)	**Statistical measures**: mean, standard deviation, skewness, kurtosis, max, min **SEF25, SEF50, SEF75, SEF95**: frequencies below which the total spectral power is found on the EMG signal during REM Sleep (Hz) **SEFd**: difference between SEF95 and SEF50 (Hz) **Average Power (AP)**: is calculated on the normalized PSD

Table 2.1: Features extracted from PSG and EMG signal. TD: time domain, FD: frequency domain

2.6.2 Model training

Automatic classification of RBD and RSWA patients was done by developing a supervised learning model. Commonly these models learn from the characteristics of previously labeled data - *training data* - and subsequently optimize their algorithm, classify known but not labeled data - *test data*. Finally, if the model performs well, then it can be used to classify unknown data. In this work, instead, since there were few subjects, the dataset was used both as training and as a test, in particular the cross-validation technique was used. The Machine Learning model used for the binary classification of unhealthy subjects (RBD and RSWA) and healthy ones is well-known Support Vector Machine (SVM) [23]. It builds a hyperplane in a multidimensional space, which, in this case, is used for classification. Its purpose is to obtain a separation of the classes so that it has the greatest distance from the closest point of each of the two classes. The generalization error of the classifier is smaller when the distance between these points is greater.

2.6.3 Performance assessment

For the validation of the model, due to the limited data available, it was decided to use cross-validation, developing the *"Leave-one-out"* algorithm. It consists in using one subject to test the model and using all the others to train it, and iteratively changing the test subject so that all subjects have tested the model at least once [24]. Employing this algorithm, performance as *accuracy*, *sensitivity* and *specificity* are calculated for each cycle on the single test subject and averaged over all cycles. It is calculated also the standard deviation.

Chapter 3

Results

3.1 Tonic and Phasic Density

For each group of subjects (Healthy, RBD and RSWA) the background muscle activity was calculated and used as a reference threshold in the algorithm for calculating tonic density and phasic density, as described in the previous chapter. The latter are calculated both with the SINBAR and with the Montréal method, but the tonic density has been reported only once because the same algorithm is used in both methods. In addition, the mean and standard deviation have been also calculated for each parameter.

The pathological threshold values are for tonic activity if it exceeds 30% and for phasic activity according to the SINBAR method if greater than 16.3% and according to the Montréal method if it exceeds 15% [19]. As expected, in Table 3.1 it can be seen that in 10 healthy subjects only one (S8) exceeds PD SINBAR and PD Montréal thresholds. As for the 10 RBD subjects (Table 3.2):

- Two subjects (RBD1, RBD3) are below the SINBAR threshold;
- Only one subject (RBD1) is below the Montréal threshold.

Instead, the 9 RSWA subjects are all below the threshold except for one (RSWA1) which is above the threshold for both the SINBAR and Montréal methods, as seen in Table 3.3.

3.2 Tonic activity envelope of the EMG signal

To graphically display the envelope of the tonic activity of the chin EMG signal, the MATLAB function *"envelope"* with *peak* mode was used in order to plot the upper and lower peak envelopes of the input signal. Another input is the number

Subject	**BKG (μV)**	**TD (%)**	**PD (%) SINBAR**	**PD (%) Montréal**
S1	0,92	0,68	7,50	6,85
S2	0,98	0,00	5,20	6,22
S3	1,40	0,00	2,02	2,22
S4	2,32	0,00	5,28	4,75
S5	0,73	3,33	7,17	7,44
S6	0,55	1,43	4,00	4,06
S7	0,85	0,00	2,24	2,40
S8	0,49	2,00	16,60	18,53
S9	0,61	0,00	11,88	11,32
S10	0,86	0,00	3,90	3,67
MEAN	0,97	0,74	6,58	6,75
STD	0,54	1,16	4,55	4,95

Table 3.1: Healthy subjects from CMS Database. Background activity (BKG), Tonic Density (TD), Phasic Density (PD) with SINBAR and Montréal method

Subject	**BKG (μV)**	**TD (%)**	**PD (%) SINBAR**	**PD (%) Montréal**
RBD1	7,94	0,00	2,89	2,52
RBD2	1,22	2,05	21,85	21,33
RBD3	2,63	0,00	14,24	15,14
RBD4	0,98	0,99	18,23	17,04
RBD5	1,04	4,27	28,63	28,49
RBD6	5,37	2,79	32,23	32,03
RBD7	2,93	25,42	37,97	41,13
RBD8	2,08	2,46	22,21	21,64
RBD9	1,95	22,93	43,89	44,33
RBD10	1,53	19,34	45,41	45,19
MEAN	2,77	8,03	26,75	26,89
STD	2,23	10,22	13,52	13,98

Table 3.2: RBD subjects from CMS Database. Background activity (BKG), Tonic Density (TD), Phasic Density (PD) with SINBAR and Montréal method

Subject	**BKG (μV)**	**TD (%)**	**PD (%) SINBAR**	**PD (%) Montréal**
RSWA1	0,55	15,53	43,29	45,63
RSWA2	1,83	0,60	6,48	6,07
RSWA3	1,83	0,00	11,04	10,56
RSWA4	0,79	2,27	14,47	14,24
RSWA5	1,34	0,00	4,77	4,24
RSWA6	0,73	0,00	8,10	7,78
RSWA7	0,79	1,63	10,49	10,92
RSWA8	3,42	0,00	6,41	5,77
RSWA9	2,87	1,44	5,54	5,52
MEAN	1,57	2,38	12,29	12,30
STD	1,02	5,00	12,04	12,91

Table 3.3: RSWA subjects from CMS Database. Background activity (BKG), Tonic Density (TD), Phasic Density (PD) with SINBAR and Montréal method

samples of peak separation, the envelope is determined using interpolation over local maxima separated by at least that samples. After some trials it was concluded that the best separation is 256 samples, corresponding to 2 seconds. In this way it does not lose information as in the case of 5 seconds and delete information that is not useful as in the envelope with 1 second separation between peaks. It should be noted that with the previously described algorithm the phasic peaks have almost all been eliminated, therefore the scale on the ordinates is different and the effect of removing the peaks is more appreciable.

Ideally the healthy subject (Figure 3.1) should have straight lines above and below the graph. The envelopes of RBD and RSWA patients are more interesting because it seems to have a periodic trend over time. The graphs are shown in Figure 3.2 and Figure 3.3 respectively.

3.3 Machine Learning

Performance of the SVM classifier using *Leave-One-Out* cross-validation are reported in Table 3.4. It can be notice that the model classifies with relatively high accuracy a RBD subject from an healthy subject (85%) and a healthy one from a RSWA patient (84.21%). However, performance drops when classification is between RBD and RSWA subjects with only 73.68% accuracy. It is also reported the Mean Percentage Error (MPE). It matches to (1 - *accuracy*).

Nevertheless, the best performances are those of the detection of RBD from

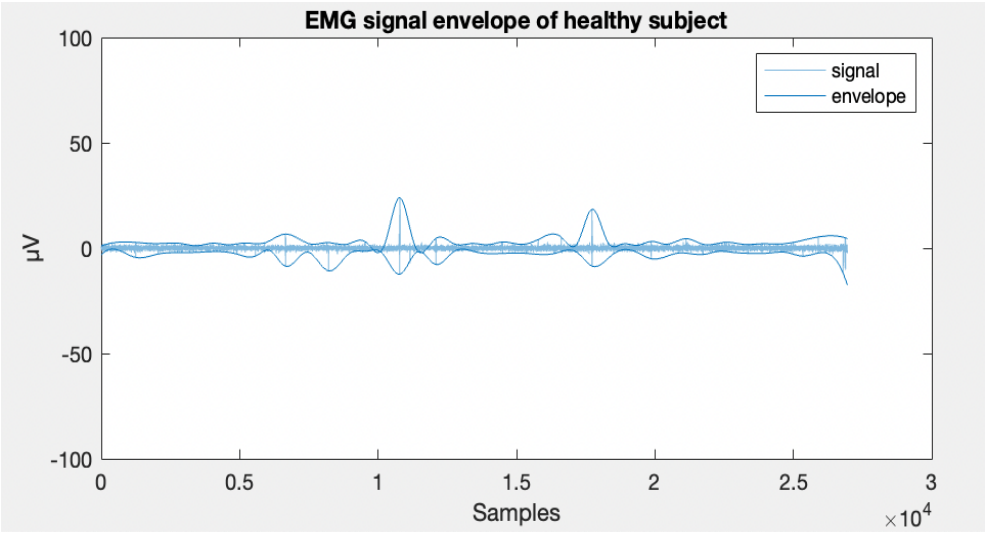

Figure 3.1: Chin EMG signal envelope of a healthy subject from CMS database

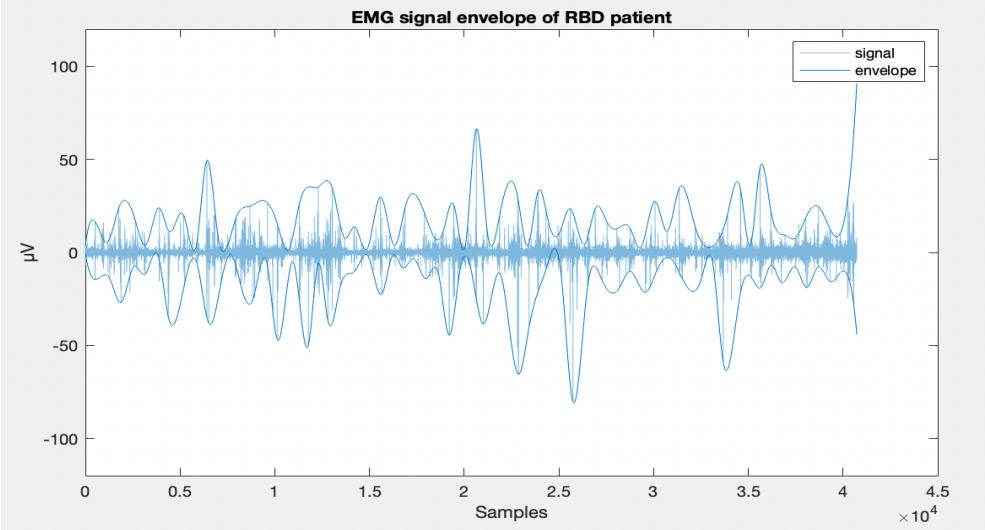

Figure 3.2: Chin EMG signal envelope of a RBD patient from CMS database

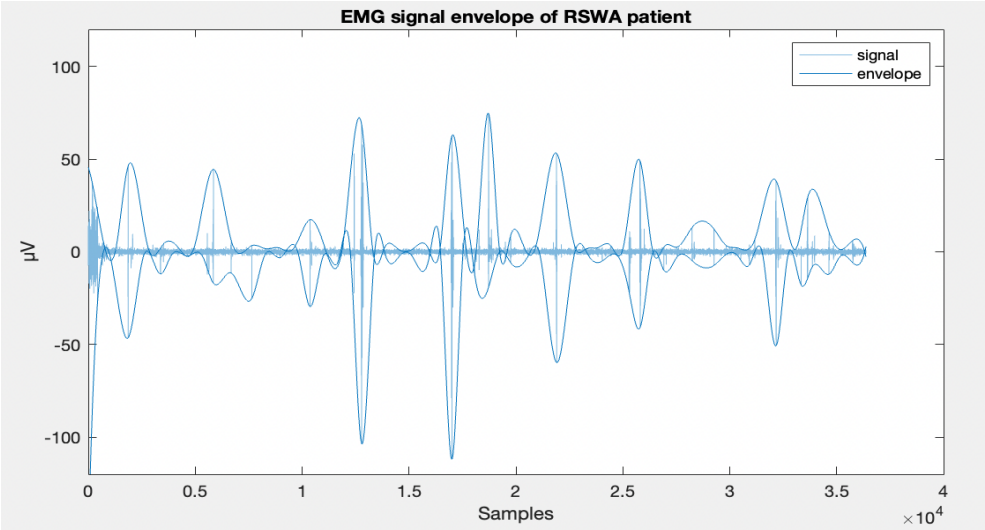

Figure 3.3: Chin EMG signal envelope of a RSWA patient from CMS database

	RBD	**RSWA**	**RBD - RSWA**
Accuracy	85%	84.21%	73.68%
Sensitivity	77.77%	75%	66.66%
Specificity	90.90%	90.90%	80%
PPV	87.50%	85.71%	75%
NPV	83.33%	83.33%	72.72%
MPE	15%	16%	26%

Table 3.4: SVM classifier performance

healthy subjects in all metrics: classification accuracy (85%), sensitivity (77.77%), specificity (90.9%), PPV (87.5%) and NPV (83.33%). These results correspond to the performance values obtained in literature [25] for RBD detection.

In Table 3.4 the columns are respectively: RBD detection from healthy subjects, RSWA detection from healthy subjects and RBD detection from RSWA patients.

Chapter 4

Discussion and Conclusion

This work proposed an algorithm capable of automatically classifying RBD based on chin EMG. RBD evaluation is essential for neurodegenerative diseases because it is considered an early stage in the development of the disease. The goal, therefore, is to anticipate the diagnosis of the onset of neurodegeneration in order to decide on a preventive curative process that can ideally prevent the onset of the disease. Currently the diagnosis of RBD requires the use of a full PSG only after the appearance of the first symptoms and this imposes a long process of diagnosis and it is therefore necessary to shorten these times. One of the precursors of RBD is RSWA; indeed, it is crucial not to allow the conversion of RSWA to RBD. It can be detected with visual scoring using the SINBAR and Montréal methods which evaluate tonic and phasic muscle activity through submental EMG signal. To automate the detection of RSWA and RBD, a machine learning algorithm has been implemented that is able to classify a healthy subject from a sick one through characteristics based on the analysis of PSG and chin EMG signal.

The tonic and phasic densities represent the percentage of REM epochs satisfying the definition of tonic/phasic over all REM epochs of the signal, according to the SINBAR and Montrèal methods. The threshold to define whether an epoch is tonic or phasic is determined by quantifying the background activity of the muscle during N3 sleep stage, the slow-wave sleep. In this study the threshold was defined as the 40th percentile of background activity but it can change giving different tonic and phasic results, in this case it is a good compromise to detect both tonic and phasic activity. In the database provided by the Sleep Disorders Center of the Molinette hospital in Turin, no subject had supra-threshold tonic density but this is not the case with regard to phasic density. In detail, as regards the SINBAR method, 10% of healthy subjects, 80% of RBD subjects and 10% of RSWA subjects had an supra-threshold value. Instead, as regards the Montréal method, 10% of healthy subjects, 90% of RBD subjects and 11% of RSWA subjects had an supra-threshold value. When the background value is high it is probably affected

by artifacts and noise and is very selective because it increases the threshold to defining the density abnormality.

Moreover, given the importance of densities in this area, they have been used as features for machine learning. Other features were extracted from the envelope of the chin EMG signal during REM sleep. The envelope of the signal was calculated only on the tonic activity around the baseline, eliminating the peaks of phasic activity. The tonic envelope on RBD and RSWA subjects was found to have a pseudo-sinusoidal periodic pattern, with a higher frequency in RBD subjects, but the cause of this pattern is not yet clear to the researchers. To complete the feature extraction, they were calculated from PSG and EMG in the frequency domain and time domain for a total of 49 features.

The whole set of extracted features was input to a supervised distance-based machine learning model, called SVM. Given the small number of subjects under examination, cross-validation with the Leave-One-Out method was used. The model proved effective in classifying RBD subjects compared to healthy subjects with an accuracy of 85%, while it was not highly effective (73.68%) as regards the classification of RBD subjects from RSWA subjects, because they have very similar characteristics. With these results it can be concluded that the model has good potential but its generalization capacity can be improved by using a database provided with other subjects and compute more features from different sources as EEG, ECG and EOG signal.

Limitations and further developments

First limitation of the study is the evaluation of the background because the results of the tonic and phasic densities depend on it, the higher the threshold through the percentile, the more specific and less sensitive the threshold will be. As far as the envelope of the tonic signal is concerned, a possible development could be to build the envelope of different muscles so as to compare their morphology and understand if there is a correlation between the morphology of the muscle in question and the disease. Furthermore, this trend could be studied more deeply by analyzing, for example, the period, the frequency, the width and the amplitude of the envelope. Finally, in the future works the ML model should be trained by extracting more features from different channels and on a larger cohort so as to be able to divide the dataset into training, validation and test and obtain more consistent and generalizable results.

Bibliography

[1] Sebastian Hitziger. *Modeling the variability of electrical activity in the brain.* PhD thesis, Université Nice Sophia Antipolis, 2015.

[2] James M Krueger, Marcos G Frank, Jonathan P Wisor, and Sandip Roy. Sleep function: Toward elucidating an enigma. *Sleep medicine reviews*, 28:46–54, 2016.

[3] Markus Dworak, Robert W McCarley, Tae Kim, Anna V Kalinchuk, and Radhika Basheer. Sleep and brain energy levels: Atp changes during sleep. *Journal of Neuroscience*, 30(26):9007–9016, 2010.

[4] Hartmut Schulz. Rethinking sleep analysis: Comment on the aasm manual for the scoring of sleep and associated events. *Journal of Clinical Sleep Medicine*, 4(2):99–103, 2008.

[5] Gabrielle Brandenberger, Jean Ehrhart, François Piquard, and Chantal Simon. Inverse coupling between ultradian oscillations in delta wave activity and heart rate variability during sleep. *Clinical neurophysiology*, 112(6):992–996, 2001.

[6] John E Hall and Michael E Hall. *Guyton and Hall textbook of medical physiology e-Book.* Elsevier Health Sciences, 2020.

[7] Birendra N Mallick, SR Pandi-Perumal, Robert W McCarley, and Adrian R Morrison. *Rapid eye movement sleep: regulation and function.* Cambridge University Press, 2011.

[8] Behrouz Jafari and Vahid Mohsenin. Polysomnography. *Clinics in chest medicine*, 31(2):287–297, 2010.

[9] Rahul K Kakkar and Gilbert K Hill. Interpretation of the adult polysomnogram. *Otolaryngologic Clinics of North America*, 40(4):713–743, 2007.

[10] Neil R Carlson and Neil R Carlson. Physiology of behavior. 2007.

[11] Michael J Thorpy. Classification of sleep disorders. *Neurotherapeutics*, 9(4):687–701, 2012.

[12] Michael J Sateia. International classification of sleep disorders. *Chest*, 146(5):1387–1394, 2014.

[13] Mark W Mahowald, Michel Cramer Bornemann, and Carlos H Schenck. Parasomnias. In *Seminars in neurology*, volume 24, pages 283–292. Copyright© 2004 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New . . . , 2004.

[14] Shantanu Singh, Harleen Kaur, Shivank Singh, and Imran Khawaja. Parasomnias: a comprehensive review. *Cureus*, 10(12), 2018.

[15] Matteo Cesari, Julie AE Christensen, Lykke Kempfner, Alexander N Olesen, Geert Mayer, Karl Kesper, Wolfgang H Oertel, Friederike Sixel-Döring, Claudia Trenkwalder, Helge BD Sorensen, et al. Comparison of computerized methods for rapid eye movement sleep without atonia detection. *Sleep*, 41(10):zsy133, 2018.

[16] Stuart J McCarter, Erik K St. Louis, and Bradley F Boeve. Rem sleep behavior disorder and rem sleep without atonia as an early manifestation of degenerative neurological disease. *Current neurology and neuroscience reports*, 12:182–192, 2012.

[17] Jacques Montplaisir, Jean-Francois Gagnon, Maria Livia Fantini, Ronald B Postuma, Yves Dauvilliers, Alex Desautels, Sylvie Rompré, and Jean Paquet. Polysomnographic diagnosis of idiopathic rem sleep behavior disorder. *Movement disorders*, 25(13):2044–2051, 2010.

[18] Birgit Frauscher, Alex Iranzo, Carles Gaig, Viola Gschliesser, Marc Guaita, Verena Raffelseder, Laura Ehrmann, Nuria Sola, Manel Salamero, Eduardo Tolosa, et al. Normative emg values during rem sleep for the diagnosis of rem sleep behavior disorder. *Sleep*, 35(6):835–847, 2012.

[19] Michela Figorilli, Raffaele Ferri, Maurizio Zibetti, Patricia Beudin, Monica Puligheddu, Leonardo Lopiano, Alessandro Cicolin, Frank Durif, Ana Marques, and Maria Livia Fantini. Comparison between automatic and visual scorings of rem sleep without atonia for the diagnosis of rem sleep behavior disorder in parkinson disease. *Sleep*, 40(2):zsw060, 2017.

[20] D Espinoza, A Ocampo-Garcés, J Diaz, E Holzknecht, A Stefani, M Bergmann, A Bassi, T Cordova, EA Vivaldi, and B Högl. Phasic coherence of forearms muscle activity: a specific measure of rem sleep without

atonia evaluated by means of envelope analysis of the electromyogram. *Sleep Medicine*, 64:S283, 2019.

[21] Irene Rechichi, Maurizio Zibetti, Luigi Borzì, Gabriella Olmo, and Leonardo Lopiano. Single-channel eeg classification of sleep stages based on rem microstructure. *Healthcare technology letters*, 8(3):58–65, 2021.

[22] Irene Rechichi, Antonella Iadarola, Maurizio Zibetti, Alessandro Cicolin, and Gabriella Olmo. Assessing rem sleep behaviour disorder: from machine learning classification to the definition of a continuous dissociation index. *International Journal of Environmental Research and Public Health*, 19(1):248, 2021.

[23] Corinna Cortes and Vladimir Vapnik. Support-vector networks. *Machine learning*, 20:273–297, 1995.

[24] Tzu-Tsung Wong. Performance evaluation of classification algorithms by k-fold and leave-one-out cross validation. *Pattern Recognition*, 48(9):2839–2846, 2015.

[25] Navin Cooray, Fernando Andreotti, Christine Lo, Mkael Symmonds, Michele TM Hu, and Maarten De Vos. Proof of concept: Screening for rem sleep behaviour disorder with a minimal set of sensors. *Clinical Neurophysiology*, 132(4):904–913, 2021.