POLITECNICO DI TORINO

Master's Degree in Biomedical Engineering

Automating REM Sleep Without Atonia Scoring Methods

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Abstract

REM Behaviour Disorder (RBD) is a parasomnia characterized by the absence of the physiologic muscle atonia during REM stage. The diagnosis of this disorder is based on the assessment of muscle activity and REM sleep without atonia (RSWA) by means of an electromyogram during polysomnography. In recent years RBD has attracted the attention of researchers because in its isolated form it is linked to the subsequent onset of neurogenerative diseases such as Parkinson's disease, dementia with Lewy Bodies and Multiple System Atrophy.

This study focuses on the analysis of polysomnographic reports from three different databases containing also RBD and RSWA patient records. Two of them were provided by the Sleep Disorders Centre of A.O.U. Molinette in Turin, Italy; while the other is created from the CAP Sleep Database, made available in open access on PhysioNet by the Sleep the Disorders Center of the Ospedale Maggiore of Parma, Italy. The polysomnographies were analysed in order to evaluate the muscular activity during REM stage with the parameters most commonly used in the clinic and known in literature for the study of REM sleep without atonia. The RSWA scoring methods chosen are as follows: REM Atonia Index (automatic, submitted by Ferri in 2008 and 2010), Montréal (visual, Lapierre and Montplasir in 1992 and 2010) and SINBAR (visual, Barcelona and Innsbruck groups, from 2011 to 2013).

An algorithm has been developed to calculate these methods as described in the literature. With regard to the visual methods, the algorithm developed is based on the criteria presented and translates the methods into automatic form. The RAI calculation method was developed and consolidated on the CAP database, and then applied to the others, while the automation of visual methods was developed in collaboration with the Sleep Disorders Centre of A.O.U. Molinette in Turin on the databases provided by them. This study outlines the results and the challenges of this automation process. One of the databases contains PSG recordings of subjects during the intake of an antidepressant drug and in its absence. The data obtained from the algorithm were used to compare the two conditions in terms of RSWA scoring.

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Chapter 1

Sleep and Atonia in Adults

Sleep in humans is a physiological state induced and regulated by the nervous system and set by the circadian sleep-wake rhythm. Voluntary activities are suppressed to make room for rest and regulatory mechanisms. The level of consciousness during sleep changes but is not necessarily related to disconnection from the external environment [1]. For this reason, it is difficult to give a complete definition of sleep. Moreover the exact function of sleep is not yet totally explored, but sleep deprivation has verified negative effects on several processes such as attention, memory, blood pressure regulation, mood regulation and many others [2]. It is shown that sleep disruption and deprivation lead to immune, inflammatory and stress response. Immune response has also been linked with cognitive impairment, but the mechanisms of the relationship are not yet fully known due to the small number of studies in humans [3]. Moreover, the quality of sleep is closely related to the quality of wakefulness, in a reciprocal relationship. The amount and type of sleep changes with age, but, in any case, about one third of life is spent sleeping.

1.1 Sleep Macrostructure

Sleep characteristics are not constant in many respects during rest, which is why sleep has been divided into stages. In order to detect these differences and detect the sleep stage, electroencephalogram (EEG), electroculogram (EOG) and electromyogram (EMG) are mainly used. Before 2007, Rechtschaffen & Kales (R&K) standardized scoring method was the most popular. Later on the guidelines from the American Academy of Sleep Medicine (AASM) took place. As the latter suggest, sleep is divided into one rapid eye movement (REM) and three non-REM (NREM) stages: N1, N2, N3. These stages define the macrostructure of sleep. In physiological sleep, the stages follow each other in a set order and once the REM stage is reached, a sleep cycle is completed. In humans, a sleep cycle lasts

approximately 90-110 min and 4-5 cycles are completed in a night. In physiological sleep, the time spent in the various stages and their succession during the night is fairly common. The first cycles are characterised by longer and more frequent N3 stages, while the last cycles by longer REM phases with more phasic activations. When sleep is disturbed, the macrostructure is altered. In the medical field, the onset of the different stages of sleep during the night is represented in a graphical layout called a hypnogram. An example of hypnogram is shown in Figure 1.1. The

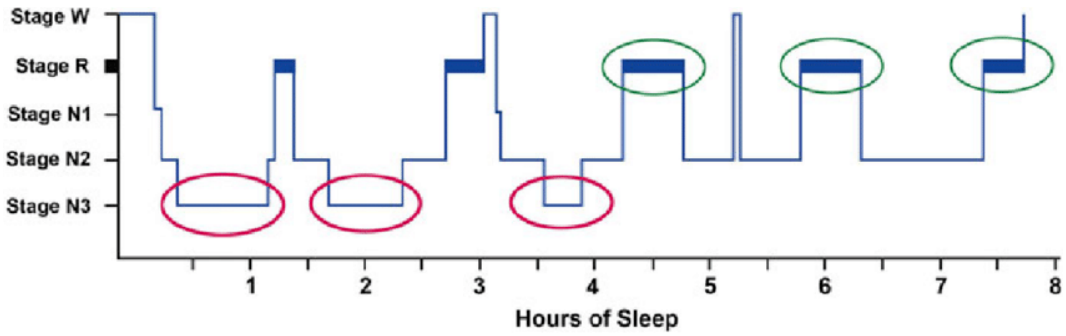

Figure 1.1: Hypnogram of normal sleep [4].

polysomnographic (PSG) recordings are observed divided into time segments. The stage scoring is done on 30s epochs. In the R&K method only one central-lobe EEG channel is used and the NREM sleep in divided in four stages. The fourth one is absorbed in the third in the AASM instruction and three (frontal, central, and occipital) EEG channels are recommended for epochs scoring. The use of multiple channels makes it possible to see certain waveforms better and thus distinguish more precisely between sleep and wakefulness and central nervous system arousals. Both methods use also one EOG derivation and submentalis EMG for scoring REM. The scoring is usually performed visually, but many automatic scoring algorithms are available and are taking place in the field. They are particularly requested because visual scoring is time consuming.

1.1.1 NREM Stages

In general, brain activity shows fluctuations that are recognisable in localised events over time. In addition, brain regions can be activated at different times. At the beginning of rest, in relaxed wakefulness, an alpha rhythm (8-13 Hz) appears in the EEG, which is recognisable in the occipital regions. When falling asleep, the frequencies of the waves begin to decrease, indicating that the activated pattern of wakefulness is being left behind. From here one moves on to the stages of NREM sleep. These stages are characterised by a progressive decrease in the frequency of the brain activity, indicating neuronal synchronisation linked to the reduced activity.

The body temperature drops as does the heart rate. The metabolic activity and blood flow are globally reduced compared to resting wakefulness. The muscle tone is progressively relaxed, but not absent. In fact, involuntary motor activity occurs occasionally, approximately every 10-20 minutes. Sensitivity to external stimuli is also lowered, so the "arousal threshold" is increased. Imaging studies suggest that this is due to the fact that activation of primary sensory areas is not transmitted to higher-order areas. Cortical connectivity is especially compromised at the level of the "thalamic gate" [1]. In these stages, also called slow-wave sleep, encephalic activity does not decrease in all areas and it is possible for the subject to think and dream. However, dreams are rare and have a less detailed, less emotional and more logical content than in the REM phase. The forebrain is responsible for the onset of slow-wave sleep and the crucial neurotransmitter is adenosine [5].

N1

Sleep officially begins when theta activity (4-7 Hz) becomes prominent in the EEG. Muscle tone begins to relax. Eye movement, which while awake with eyes closed shows both slow and fast activity, becomes slow and circular.

N2

Shortly afterwards, the N2 stage usually starts. The theta rhythm is still prominent. N2 can be recognised by certain events in the EEG of the central regions: sleep spindles and K-complexes. Sleep spindles are portions of the EEG trace with a frequency typically of 12-15 Hz and duration of about 1s occurring several times a minute.Their amplitude first rises and then falls. A K-complex is a recognisable waveform, characterised by a narrow peak followed by a slow one of opposite sign with amplitudes that stand out from the background activity.

N3

The main frequency range in the EEG becomes the theta range (0.5-2Hz, higher amplitude). Eye movement and muscle activity decrease further, while the arousal threshold increases. in Figure 1.2 the different EEG frequency rhythms and typical waveform of all NREM stages are shown.

1.1.2 REM Stage

This stage is the last of the cycle and differs greatly from the others, in fact, it is sometimes referred to as paradoxical sleep because of its similarity to the waking state. Paradoxical is also the fact the arousal threshold is the highest, but it is the time when one is most likely to wake up spontaneously. The most intense

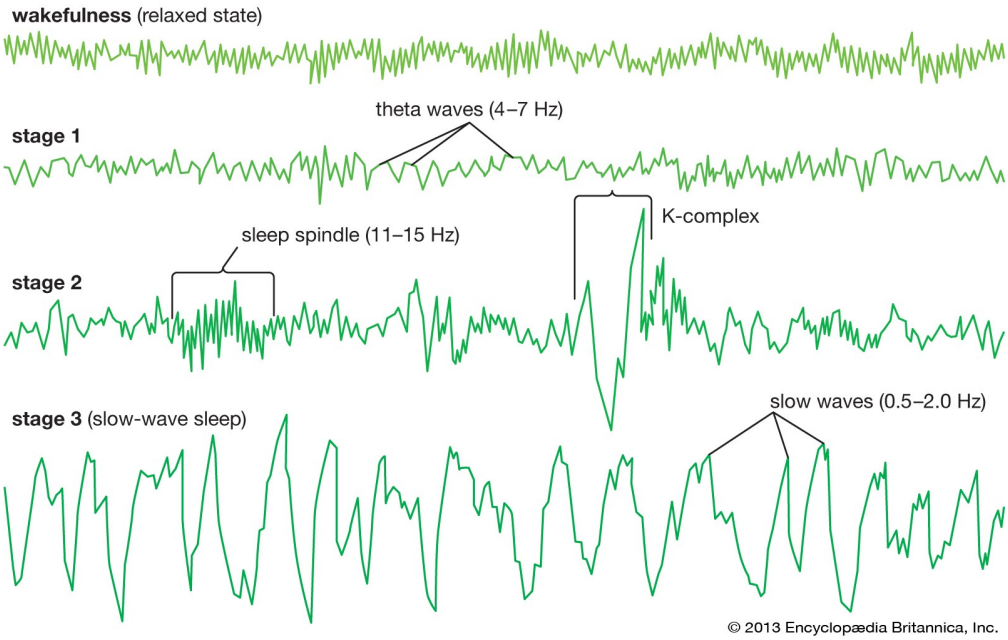

Figure 1.2: Electroencephalogram showing typical brain waves of sleep and wakefulness [6].

and involving dream activity takes place here. Rapid eye movements (REMs), which give the stage its name, are defined as conjugate, irregular, sharply peaked eye movements with an initial deflection usually lasting < 500 ms in The AASM Manual [7]. The pons is responsible for the onset of REM sleep and the crucial neurotransmitter is acetylcholine [5].

REM stage is not further divided into phases, but tonic and phasic phenomena are usually distinguished in it. Phasic phenomena occur episodically. Between tonic phenomena there are:

- EEG that shows desynchronised activity with mixed frequencies, similar to that of wakefulness. A theta rhythm is recognisable especially in the area of the frontal cortex and the midline. Other distinctive waves are sawtooth waves (triangular, 2-6 Hz) and PGO waves (Ponto-Geniculus-Occipital) which occur as isolated large amplitude potentials just before the REM sleep onset.

- At muscular level there is atonia, i.e., a total loss of muscle tone. This allows the subject to remain motionless despite intense brain activity. Exceptions are the medial extraocular (that produces REMs), the middle ear and the diaphragm. REMs are characterised by both tonic and phasic phenomena. The tonic one is the combination of the relaxation of the rectus muscles and the tonic contraction of the medial one that causes the eyes to converge

downwards.

- Blood pressure rising;
- Homeostatic thermoregulation mechanisms, such as sweating, stopping;
- Pupils constriction;
- Erections.

Between phasic phenomena there are:

- Rapid eye movements presence both in isolation and in bursts;
- Irregular breathing;
- Irregular heartbeat;
- Middle ear contraction;
- Twitches.

1.1.3 Sleep Microstructure

Scoring 30s epochs for sleep stages fully describe the macrostructure of sleep, but it is not able to report information about short-duration events. Within the individual NREM stages, a distinction can still be made between CAP (Cyclic Alternating Pattern) and non-CAP (NCAP) sleep periods. This distinction describes the microstructural organisation of sleep and summarises the micro-events. The microstructure of sleep interacts with the expected sleep pattern and represents the body's adaptation to the internal and external conditions that occur during sleep, modifying rapidly the level of consciousness and vigilance. During CAP periods, sleep is dynamic. The polysomnographic traces oscillate between a greater depth of sleep, also called phase B, and moments of lightened sleep during which arousals or even imperceptible micro-awakenings occur, called phase A. Phase A can be classified into three subtypes that generate more or less marked increases in vegetative activities, e.g. pulse [8]. On the contrary, NCAP periods are characterised by a homogeneous tracing and a constant sleep depth level. The CAP is physiological and helps to give an indication of the type and quality of sleep, in fact it reflects the instability of the arousal level. The percentage of CAP indicates the quality and stability of sleep. A value that is too high indicates unstable, and therefore disturbed, sleep.

Regarding REM microstructure, the tonic and phasic phenomena listed before are also seen as two different microstate. Is suggested that "Tonic periods are intermediate states between phasic REM sleep and wakefulness with respect to

external information processing. Whether this restored environmental alertness is restricted to simple tasks such as auditory discrimination or enables more complex processing, possibly even learning is still unexplored and remains a generally controversial issue in sleep research" [9].

1.2 Sleep Disorders

Sleep disorders are very numerous and differ in many ways. For this thesis work, REM Behaviour Disorder (RBD), which is part of the REM sleep parasomnias, is of particular relevance. However, many elements of other disorders and phenomena have to be taken into account in research about this topic. The purpose of this paragraph is to outline the general issue and to collect all the elements that will be useful for the following discussion.

Sleep can be disturbed by a number of factors: physical, psychic, circadian and environmental disorders or by psychotropic substances. Whatever the disturbing element, sleep is progressively deconstructed. First the microstructure changes, sleep becomes more unstable and the CAP rate increases. Then there may be alterations in the macrostructure until sleep is fragmented with the appearance of several awakenings of varying length. This creates sleep deprivation in both quantity and quality.

To classify sleep disorders, reference is made to the *International Classification of Sleep Disorders* (ICSD) published by the American Academy of Sleep Medicine (AASM) in its latest version of 2014: ICSD-3. The manual contains diagnostic criteria as well as symptoms, etiology, pathophysiology and treatment. It groups a total of 59 sleep disorders into 7 main sections:

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.

Parasomnias are a group of sleep disorders characterised by dissociation state, i.e., some features of the sleep stage are impaired or exchanged for another. This results in the occurrence of non-physiological and often unpleasant behaviour or

sensory experiences. The most common are sub-classified according to the stage that is disturbed: disorders of arousal (NREM sleep), REM parasomnias and corresponding to the transition between stages [10]. REM parasomnias are:

- Nightmare Disorder: intense dreaming becomes terrible nightmares that occur in REM stage or N2 and result in awekening;
- Recurrent Isolated Sleep Paralysis: the atonia, peculiar to REM stage, occurs also in the sleep-wake transition;
- REM Sleep Behavior Disorder: the atonia, peculiar to REM stage, is lost.

RBD is central for the development of this work and is further discussed in the next section.

1.2.1 REM Behaviour Disorder

RBD is a parasomnia characterized by the absence of muscle atonia during REM phase. This can lead to the patient's enactment of dreams (dream-enactment behaviors), with the risk of endangering themselves or the bed partner. Usually the content of the dreams is violent and emotionally involving, so, as an example, the patient reproduces the movements of a kick, a heated argument or an escape. Cases of potentially lethal behaviour such as choking, bed falling or defenestration have been reported in literature [11]. Males are more affected and the average age of onset is beyond middle age. The population prevalence is estimated around the 1% for the age group of more than 50-60 years [12]. It is assumed that the vast majority of RBD cases go undiagnosed, in fact dream enactment is thought to become more evident when the content is violent (on average more often in men) and in the presence of a bed partner who notices the behaviour (on average women outlive men). It is in these cases that the subject seeks medical advice that then leads to the diagnosis. In addition, observation of video polysomnographies has allowed video classification of motor events, and studies conducted in this regard appear to show that, even in the most severe cases of RBD, motor events are more likely to be simple and low-amplitude rather than violent, suggesting that the latter are only the most alarming and easily recognisable and therefore best known to the literature [13].

Chronic RBD is given by the failure of spinal motor neuron inhibition. This can be due to α-synuclein and other forms of neurodegeneration, narcolepsy, structural pontine lesions, medications (especially antidepressants) and it is also associated with paraneoplastic and autoimmune encephalitides. RBD is present in 25–58% of patients with Parkinson"s disease, up to 90% of those with Dementia with Lewy Bodies (DLB) and up to 100% of those with Multiple System Atrophy (MSA) [12]. In 60% of cases it is idiopathic [14]. Idiopathic RBD (iRBD) has recently been the

subject of numerous studies and is now firmly associated with the development of neurodegenerative diseases. In fact, the currently calculated risk of conversion to an α-synucleinopathy from an iRBD is more than 80% after 10 years and in any case biomarkers of neurodegeneration are present [15]. Consequently, iRBD is now considered to be a symptom of α-synucleinopathies that appears many years before the others and is commonly referred as isolated RBD instead of idiopathic (also cryptogenic). It has therefore prompted great interest both in the study of neurodegeneration development and in neuroprotective trials. Since RBD occurs both years before and after the diagnosis of these diseases, the relationship with neurodegeneration is still unclear. One hypothesis is that there is a subtype in which neuronal damage begins in the areas that regulate atonia so that RBD is the prodromal clinical manifestation of the disease [12]. Furthermore, as regards PD, there is evidence in the literature that PD together with RBD (PDRBD+) corresponds to more severe parkinsonian symptoms, autonomic dysfunction, and cognitive impairment, suggesting the existence of a malignant clinical phenotype [16]. This further increases the importance of diagnosing RBD even in the presence of other pathologies that may already alter sleep characteristics.

The diagnosis of this parasomnia uses the characteristics of the electromyographic signal, as specified by the ICSD diagnostic criteria. The diagnostic criteria for RBD proposed by the*International Classification of Sleep Disorders* (ICSD)-3 [17] are the following:"

1. Repeated episodes of sleep-related vocalization and/or complex motor behaviors.

2. These behaviors are documented by polysomnography to occur during REM sleep or, based on clinical history of dream enactment, are presumed to occur during REM sleep.

3. Polysomnographic recording demonstrates REM sleep without atonia (RWA).

4. The disturbance is not better explained by another sleep disorder, mental disorder, medication or substance abuse. "

These must be fulfilled for a definitive diagnosis and necessarily include polysomnography and REM Sleep Without Atonia (RWA or RSWA) assessment. The latter is crucial in diagnosis and numerous methods have been developed and refined over time. These are based on the evaluation of the electromyographic signal of one or a group of muscles and the quantification of tonic and phasic muscle activity occurring in REM phase. ICSD-3 mentions reference cut-off values at the present time, but this will be detailed in the Section: "RSWA quantification methods". Several questionnaires have been proposed to try to avoid PSG, but due to the risk of misclassification these are only used as screening or as a diagnosis of "probable

RBD" [13]. These criteria are crucial for diagnosis given the fact that there are several conditions that mimic RBD: "different conditions may mimic RBD, the most frequent being obstructive sleep apnea during sleep, non-REM parasomnia, and sleep-related hypermotor epilepsy. These diseases might also be comorbid with RBD, challenging the evaluation of disease severity, the treatment choices and the response to treatment evaluation" [18]. In fact, RSWA assessing goes through the collection of electromyographic signals and it is influenced by other nocturnal events that cause movement such as Periodic Leg Movement (PLM) or Restless Leg Movement (RLM).

1.3 How Sleep Is Studied

Clinically, there are different approaches to the diagnosis and treatment of sleep-related symptoms. They include history and questionnaires, physical examination, laboratory tests and nocturnal polysomnography. In fact, as illustrated in the previous section, sleep characteristics can be investigated by recording bioelectrical signals. Mainly of interest are EEG, EMG, EOG and respiratory or cardiac signals in the presence of disorders related to them. Sleep monitoring is necessary in the diagnosis of the most frequent sleep disorders such as: Insomnia, Snoring and Obstructive Sleep Apnea Syndrome (OSAS), Bruxism, Restless Legs Syndrome, Sleep Epilepsy, Sleepwalking, Narcolepsy and Sleep Disorders in Children. The most comprehensive and routine monitoring is done by polysomnography (PSG). The characteristics of this diagnostic test are explained in the next section. Regarding RBD and atonia studies, PSG is the required test because it is complete and allows the evaluation of REM Sleep Without Atonia (RSWA). Other common types of sleep studies are actigraphy, Positive Airway Pressure (PAP) titration study, Multiple sleep latency test (MSLT), Maintenance of wakefulness test (MWT). Many evaluations can be done with these tests' results.

1.3.1 Polysomnography

Polysomnography (PSG) is a diagnostic test that, as mentioned before, allows both the macro and micro structure of sleep to be appreciated. Polysomnography is the gold standard in the study of sleep and in the diagnosis of various disorders. Guidelines about when and how PSG is to be used are present in clinical practice. PSG involves the simultaneous recording of several signals, is conducted overnight at a sleep study center or other designated site by sleep technicians. Bio-signals recorded include at least 3 EEG channels, submentalis EMG, EOG, EKG and signals regarding respiratory function in order to evaluate breathing related sleep disorders. Bio-signals have particular characteristics and often low voltage. In addition, they are sometimes superimposed in band, making it difficult to isolate

them. For this reason, ad hoc techniques have been developed to optimise the sampling of each signal and are now well established. In general, the sampling of signals takes place through a setup defined by:

- The configuration of the electrodes: referential recording (EEG, EOG, EMG), true bipolar recording (EKG in PSG, thermal flow), DC recording (nasal pressure, SpO_2). Referential recording is usually used when the signal amplitude is very low and very susceptible to noise. The common mode rejection amplifier configuration is exploited. Amplifiers amplify the difference between two signals, in this case what is common on both signals (background noise, DC, AC power lines) will be deleted, moreover all the amplifiers are referred against the common ground (e.g. forehead for EEG channels). Impedance balancing is essential to exploit this effect, so the type of electrode also has an influence. Usually a derivation is displayed, i.e. two channels are subtracted so that the common reference is deleted and the difference of the two signal is shown on display. This is done digitally for observation purposes only, in case of an electrode went bad it is possible to observe another derivation. If the reference electrode is faulty all the others are affected;

- Sampling rate and A/D conversion features;

- Monitor resolution, which is particularly important in the case of PSG since very different signals are shown together in a certain time window that runs during the recording. This can produce aliasing so is suggested to change the time window of observation to see if there are strong changes in the shape of the waves. Display screens definition suggested is 1600×1200 pixels;

- Hardware and software filtering.

Detailed recording recommendations of how to perform PSG and what to do in different scenarios are provided by AASM in *The AASM Manual for the Scoring of Sleep and Associated Events* [7]. There they provide indications about how to setup electrodes or recording settings. Recording recommendations for Digital Polysomnography extracted from AASM standards manual and adapted in *Principle and Practice of sleep medicine* [19] are shown in Figure 1.3. To record the EEG, EOG, and EMG, electrodes are placed on the scalp and skin surfaces. The spot is cleansed and properly prepared to ensure good contact and ensure the right electrical impedance. Usually a conductive gel is applied. EEG recording in PSG requires the recording of at least 3 derivatives: frontal, occipital, central (8 electrodes). This allows observation of overall brain activity (from the scalp) and scoring of sleep stages and arousals. As already said, those are recorded by differential AC amplifiers in referential recording mode. The electrodes are positioned according to the American Electroencephalographic society's international 10-20 system,

Recording Recommendations for Digital Polysomnography

Recording Channel	Sampling Rate (Hz)* Desirable	Sampling Rate (Hz)* Minimal	Filter Setting (Hz) Low *f*	Filter Setting (Hz) High *f*
Central EEG (C4-M1)	500	200	0.3	35
Occipital EEG (O4-M1 or Cz-Oz)	500	200	0.3	35
Frontal EEG (F4-M1 or Fz-Cz)	500	200	0.3	35
Left EOG (E1-M2 or E1-Fpz)	500	200	0.3	35
Right EOG (E2-M2 or E2-Fpz)	500	200	0.3	35
Muscle tone (submental EMG)	500	200	10	100
ECG (lead II, modified)	500	200	0.3	70
Airflow sensors at nares and mouth	100	25	0.1	15
Oximetry (ear lobe or finger)	25	10	0.1	15
Nasal pressure	100	25	0.1	15
Esophageal pressure	100	25	0.1	15
Body position	1	1		
Respiratory effort				
Snoring sounds	500	200	10	100
Rib cage and abdominal movement	100	25	0.1	15
Intercostal EMG	500	200	10	100

E1, Left eye; E2, right eye; ECG, electrocardiogram; EEG, electroencephalogram; EMG, electromyogram; EOG, electrooculogram; *f*, frequency; Fpz, frontal pole; M, mastoid.
*Higher sampling rates increase file storage requirements but provide increased temporal resolution. The tradeoff between fidelity and practicality is a matter of debate.

Figure 1.3: Recording recommendations for Digital Polysomnography [20].

whereby the electrodes are placed according to a Nasion Inion percentage distance (anatomical repere). The position of each electrode on the scalp is indicated by an abbreviation, which is also referred to in the guidelines. Recommended positions are F_4, F_3, C_4, C_3, O_2, O_1, M_1, M_2. Moreover, amplifiers require calibration both at the beginning and the end of the recording. This verifies that amplitude changes of the recorded signal really reflect changes of the brain activity. EOG recording in PSG requires the recording of two derivatives (4 electrodes): E_1, E_2, M_1, M_2 EOG voltages are higher than EEG signals because there is no bone attenuation. EOG placement was on the outer canthus of the eye: 1cm above it on right side (ROC) and the other 1cm below it on left side (LOC). AASM recommendations suggest E_1 and E_2, the respective positions are shown in Figure 1.4. The signal is due to the polarity of the eye, in fact the cornea (front) has a positive polarity while the retina (back) has a negative one. When the eyes moves, retina and cornea move closer to/farther from the electrodes causing a voltage variation. A schematic representation of the signal behaviour in both recommended and alternate configuration is shown in figure 1.5.

EMG in PSG is recommended for evaluating muscle tone and limb movements. For example, chin EMG is used for assessing atonia during REM stage (and so recognising it) while leg movements are used for Periodic Limb Movement evaluation or RLS diagnosis. Submental (chin) EMG is the gold standard for recording muscle

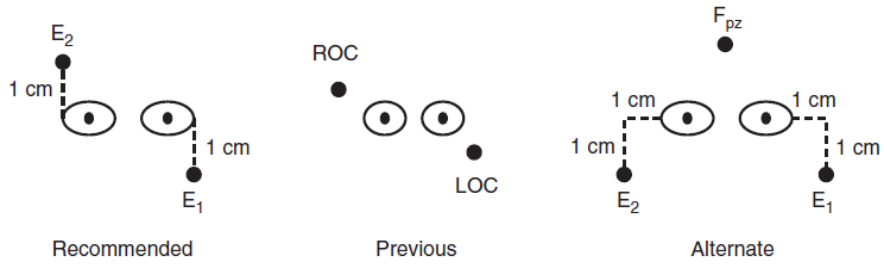

Figure 1.4: Recommended, previous, and alternate eye movement electrode positions. LOC: left oute canthus; ROC: right outer canthus [21].

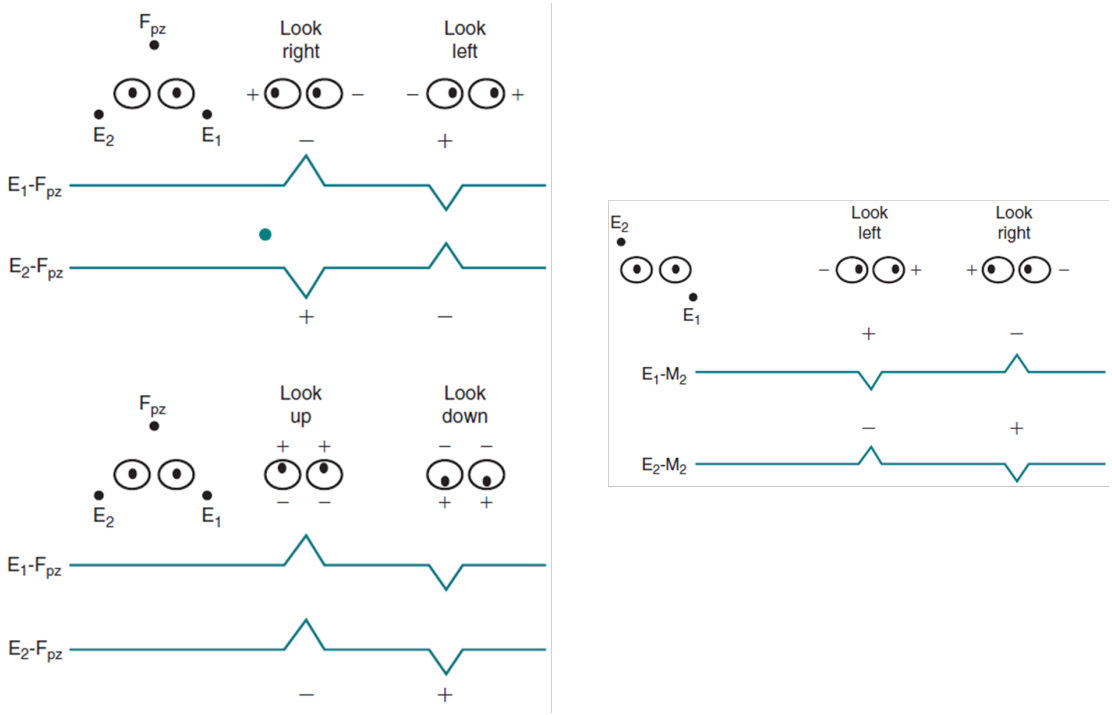

Figure 1.5: On the right, schematic deflections in E_1 - M_2 and E_2 - M_2 from eye movements [21]. M_2 stays for right mastoid and it is the reference electrode. On the left Schematic deflections in E_1 - Fpz and E_2 - Fpz (alternate setup) due to horizontal and vertical eye movements [21]. Fpz is used as reference electrode.

tone and staging REM stage. Electrode positions are usually indicated by chin1, chin2 and chin3 eventhough there is not a standard name. Three electrodes are recommended: midline 1 cm above interior edge of mandible, 2 cm below inferior edge of mandible and 2 cm right of the midline, 2 cm below inferior edge of mandible and 2 cm left of the midline. A drop in muscle tone is expected in REM stage:

"The reduction in the chin EMG amplitude during REM sleep is a reflection of the generalized skeletal-muscle hypotonia present in this sleep stage" [21]. An example of the falling chin EMG amplitude just before the REM stage onset in shown in Figure 1.6 from *Fundamentals of Sleep Medicine* by Berry. Moreover in the PSG setup two electrodes on the anterior tibialis (right and left) are added in order to detect leg movements. As already mentioned, the respiratory conditions are also

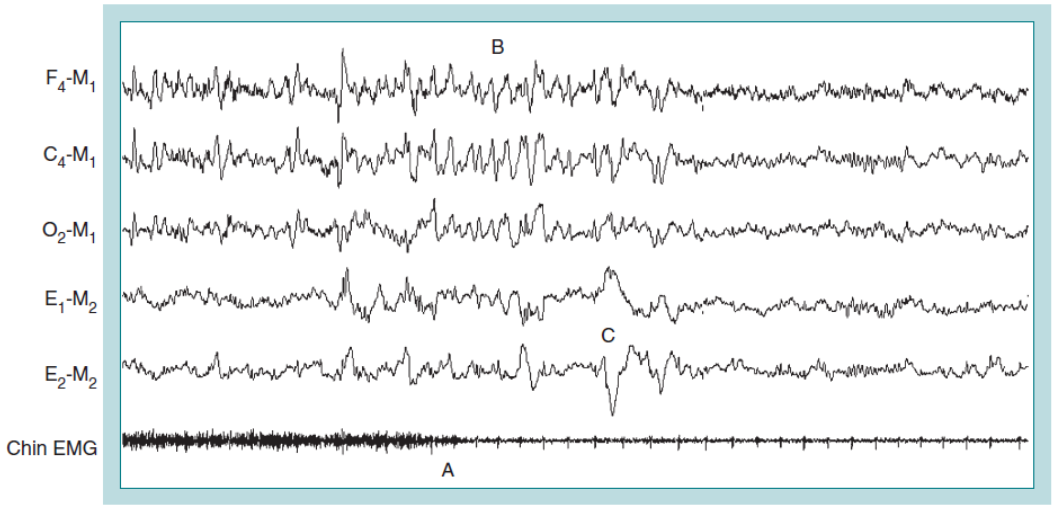

Figure 1.6: A 30-second tracing shows a reduction in the chin EMG on transition to REM stage (A). It is also possible to see saw-tooth waves just before the R stage onset (B) and REMs (C) [21].

evaluated, e.g. in search of apnea or observing breath rate for sleep staging and interference. For this reason respiratory flow, respiratory effort, saturation as well as ECG are recommended channels. To asses behaviour aspects it is possible to perform video-polysomnography. After the recording of the signals and subsequent analysis, the assessments of different parameters is carried out: sleep staging, sleep efficiency, sleep onset latency, arousals, breathing and cardiac abnormalities, leg movements, sleep fragmentation, sleep quality, sleep disorders diagnosis and differential diagnosis.

PSG Alternatives

Regarding PSG it is important to emphasise that it is a painless examination free from side effects, however it presents with some significant complications for both the patient and the technicians who has to complete the report. The equipment required is voluminous and expensive and therefore not portable; this examination

can only be performed in suitable centres. The patient's sleep is made difficult by the presence of the equipment and unfamiliarity with the location, which often forces the examination to be repeated on several consecutive nights [22]. For the healthcare facility, this means committing space and instrumentation over a long period of time and also involving an operator in completing the classification into sleep stages of 5-10 hours of recordings. It also requires skilled sleep technologists. For these reasons, both simplified polysomnography (PSG) kits that can be taken at home and algorithms for automatic classification of sleep stages and/or recognition of various disorders are being studied [23], [24], [25], [26]. Examples of technologies that can substitute PSG in certain cases are actigraphy, audio recording, OSA home assessing devices, PSG home monitoring [27], [28], [29], [30], [31], [32], [33], [34]. Regarding novel techniques for identifying sleep mechanisms and disorders genetic and optogenetic ones are catching on.

1.3.2 RSWA Quantification Methods

As already mentioned, the diagnosis of RBD is based on the finding of abnormal electromyographic activity. In particular, elevation of the muscle tone, both tonic in the chin, i.e. maintained, and phasic in the limb. These parameter has shown high stability, but at the beginning (till ICSD-2) was not specified how to quantify the elevation or rather how to quantify the absence of muscle atonia. Moreover, it was not specified which muscles should be taken into account for the analysis. Therefore, several methods to quantify REM Sleep Without Atonia have been developed. The first and currently in use in the clinic are visual scoring methods: Montréal and SINBAR. Many automatic parameters were proposed and presented in literature to replace/ support visual methods such as the REM Sleep Atonia Index (RAI) or the supra-threshold REM EMG activity metric (STREAM) ,[35], [36]. Currently ICSD-3 contains SINBAR group indication. These methods are used in general to study and evaluate Atonia. Interest in this topic has grown over time, given its link to neuroregeneration. The current objective is to find effective, objective and more rapidly assessable descriptors of atonia that can lead to the early detection of pathological features. It is hoped to be able to describe the evolution of the RSWA condition over time with these variables.

Visual scoring

Visual scoring methods are based on the quantification of phasic, tonic and any muscle activity. In literature cut-off value for each method are present. They indicate the values above which the detected activity is abnormal and therefore demonstrates RSWA [37]. All methods use at least one chin electromyographic channel recorded according to recommendations (10-100 Hz filtering). The signal

is carefully examined for artifacts of various types: due to instrumentation, patient movements or related to specific patient pathologies. If the signal is severely compromised, the epochs are excluded from the analysis. The signal under examination is rectified. Methods, definitions and cut-off values are summarised in the table shown in Figure 1.7. As can be seen, these methods are based on amplitude thresholds of the electromyogram. Subject-specific background activity defined as the minimum activity (amplitude) detected in non-REM sleep is used as reference.

The SINBAR group has presented numerous papers in literature on this topic and is, as noted above, taken as a reference. Over the years, it first established new cut-off values, then examined all possible combinations of muscle channels in order to maximize the diagnostic value of the parameters [38], [39]. In the end, the combination of two muscles recordings showed the best performance: the submentalis muscle and the bilateral Flexor Digitorum Superficialis (FDS). They recently use automatic density parameter scoring software based on their criteria and validated by them.

1.4 The Future of RSWA Scoring

The analysis of polysomnographies is always complicated as the signals are recorded for several hours, consequently any kind of evaluation on them is time consuming. It is therefore evident that in this field much of the research is focusing on trying to automate the procedures for analyzing or at least skimming this type of examination. In this work, the scoring procedures of sleep stages and those of RSWA scoring have been described. As regards the former, in literature and in commerce there are already validated softwares in use for a long time and on a large scale that automate the procedure. While for the latter, although options have already appeared on the market, it is still in the midst of research. In this case, the scoring methods are based on amplitude thresholds. This mainly creates three types of difficulties in the direct automation process:

- The amplitude is affected by noise and interference that are impossible to remove completely without compromising the signal content or significantly increasing the complexity of the processing. In the case of polysomnography, the recording of the signal takes place for several consecutive hours, accentuating this problem. In addition, the subject may move and detach electrodes, causing significant amplitude jumps. These types of events have little impact on the evaluations from the expert eye of a sleep technician, who readjust the criteria to the changes in the signal they recognise, whereas on a threshold-based algorithm this issue has a strong impact;

- The signal processing applied to the signal can strongly affect the amplitude.

Filter with the same purpose and nominal features, but different implementation can lead to different amplitude variations. For this reason it is important to verify the type of processing applied when using amplitude thresholds and amplitude based criteria. Information about the type of implementation of the filter used are not reported in literature;

- The thresholds chosen are based on the visual assessment that an operator makes when looking at the signal, not on an objective quantification of the information present. Moreover "Surface EMG is an uncalibrated signal, which is believed to show large inter- and intra-individual variability, even during the same recording; for this reason, it is very difficult to consider its absolute amplitude as a parameter for quantitative analysis" [40]. This causes intra- and inter-individual variability in both threshold and scoring evaluations. It also makes it necessary to translate the recommended criteria into quantitative rather than qualitative terms, for example in the use of the terms "average", "minimum" and "maximum";

- The amplitude may be affected by physiological phenomena characteristic of the subject and his specific pathologies. Again, operators are familiar with these phenomena and knows how to recognise and distinguish them from the phenomena under investigation, whereas the algorithm would need a considerable increase in complexity to achieve the same goal.

For these reasons, the most modern automatic classification methods, such as artificial intelligence, are taken into account in implementing these classification algorithms. Many attempts have been already made to automate scoring [41], [26], [42]. More or less sophisticated methods can be considered. Supervised and unsupervised, automatic or semi-automatic. However, this type of implementation separates itself from the clinical definitions and methods described in medicine, because it directly exploits data. This requires further clinical validation from the staff, as they are responsible for the diagnosis/information provided by the algorithm. If the basis on which this decision is made is not clear, healthcare staff will be reluctant to use it. From this, RAI and many others automatically scored parameters already cited, immediately comprehensible, were developed. Although attempts to bypass the classical methods of RSWA quantification are present in literature, especially with regard to the role of RSWA and RBD related to degeneration and thus its predictive and descriptive value of the evolution of neurodegenerative diseases [16], [43], [44]. Another problem with these polysomnographic applications is that there is not a lot of data available. For example, in the case of RSWA scoring, the algorithm must be able to correctly classify tonic and phasic epochs regardless of the patient's pathology, so databases of polysomnographic recordings of RBD patients, RSWA, controls, OSA, PD (etc.) may be required. In addition, the

validation or training of the algorithms requires that the scoring of both sleep stages and RSWA is done by technicians. As already mentioned, these are extremely time-consuming procedures, which in the clinic are carried out with more approximation unless there are research purposes. For all these reasons it is difficult to find sufficiently large and sufficiently complete databases. Therefore, in this thesis work the algorithm developed follows as closely as possible the indications in literature for developing each method. With regard to the limitations of amplitude-based methods described above, the algorithm presented here also showed considerable susceptibility. It was decided mainly to focus on two elements: the estimate of the background activity value (BKG) and the effect of the ECG artefact. In fact BKG activity is established once and for all for each patient and corresponds to an amplitude value. In the clinical practice, however, in addition to being a value already not unique in itself and defined only qualitatively, technicians often readjust the definition according to the trace, for example based on artifacts or peculiar waveforms. The EKG, on the other hand, is a complex artefact to remove as it is superimposed in band to the EMG signal. Depending on the sampling setup and the patient, the amplitude of the EKG can be very visible. In this work, a method is implemented to reduce this artefact without frequency filtering (thus modifying the entire signal). The effects of this parameters on the algorithm are described in the following chapters.

1.4.1 RAI

One attempt to overcome visual scoring methods problems and to have a strictly quantitative evaluation of atonia is Ferri's REM Atonia Index. This indicator is also based on the amplitude of the electromyographic signal. Ferri demonstrated its effectiveness in distinguishing pathological cases of RBD and MSA from healthy subjects using a threshold he proposed and thus revealing its potential diagnostic use [40], [45]. However, it is not yet clear whether this index can be used as the sole descriptor of the condition of atonia or of the evolution of the subject's condition. RAI is calculated on the submentalis muscle EMG channel. The signal is band pass filtered 10-100 Hz according to recommendations, a 50 Hz notch filter is also used. The signal is rectified. The classic 30 s sleep epochs are divided in 1-s mini-epochs. For each mini epoch the average amplitude (AA) is calculated. RAI is calculated as the ratio between the number of EMG mini-epochs with average amplitude $\leq 1\mu$V and the total number of mini epochs (excluding those with 1 μV$<$ AA $\leq$2 μV). Thus, the RAI takes on values ranging from 0 (no small amplitude epochs, i.e., total absence of atonia) to 1 (perfect atonia). This choice stems from the observation of the normalised distribution histograms of the AA, in fact using amplitude intervals such as 1 μV$<$ AA $\leq$ 2 μV, 2 μV$<$ AA $\leq$ 3 μV,..., AA $>$ 20 μV as bins, it is possible to see how often the mini-epochs assume an amplitude

in a certain amplitude interval. In particular, in atonia it can be seen that the amplitude usually does not exceed 1 microvolt, thus increasing the first bin. On the contrary phasic and tonic activations, increasing the average amplitude of the EMG, will be represented by the increase of the successive bins. Observation of these histograms also made it possible to note the strong influence of age on the characteristics of the signal amplitude and therefore of the condition of atonia that it describes.

In 2010, Ferri published an improved version of RAI computation, whose aim is to reduce noise [35]. This consists in subtracting from the AA calculated on the mini-epoch a value obtained as the minimum value present in a window of 60 seconds around the epoch under examination. This subtracted value represents the estimated background noise in that window. The computation procedure is otherwise unchanged from the first version. With this method all young controls showed AI>0.9, aged controls AI>0.8, MSA AI<0.8, 74,4% of iRBD AI<0.9 [35].

	Montréal			SINBAR		
	Tonic	**Phasic**	**Any**	**Tonic**	**Phasic**	**Any**
EMG Channel	Chin	Chin	-	Chin	Chin and FDS	Chin and FDS
REM Epoch Length	Originally 20s adapted to 30s	2s	-	30s	3s	3s and 30s
Epoch Scoring	More than 50% of the epoch shows activity with amplitude more than 2 times the **background activity** or more than 10 µV	The epoch is phasic if it contains EMG bursts of **0.1-10s** with amplitude **4** times the **background activity**	-	More than 50% of the epoch shows activity with amplitude more than 2 times the **background activity** or more than 10 µV	The epoch is phasic if it contains EMG bursts of **0.1-5s** with amplitude **2** times the **background activity**	Either tonic or phasic (or both together) in the same channel or in both
Density	Percentage of tonic epochs out of the total number of REM epochs	Percentage of phasic epochs out of the total number of REM epochs	-	Percentage of tonic epochs out of the total number of REM epochs	Percentage of phasic epochs out of the total number of REM epochs	Percentage of 'any' chin epochs on total REM. Percentage of 'any' chin epochs with also bilateral phasic FDS activation (Chin+FDS Density) in 3s or 30s epochs out of total REMs.
Cut-off Values	Tonic Density ≥ 30%	Phasic Density ≥ 15%	Tonic Density ≥ 30% and/or Phasic Density ≥ 15%	Tonic Density ≥ 30%	Phasic Chin Density ≥ 16.3%	'Any' Chin Density ≥ 18% Chin+FDS Density (3s) ≥ 32% Chin+FDS Density (30s) ≥ 27%[1]

REM= Rapid Eye Movement, EMG=Electromyogram, FDS=Flexor Digitorum Superficialis.
[1] The 27% threshold is also reported in the ICSD-3 as the most evidence-based data. All the values are presented in literature [17], [36].

Figure 1.7: Visual RSWA scoring Methods: Montréal and SINBAR.

Chapter 2

Materials and methods

2.1 Database

2.1.1 CAP

The CAP Sleep Database is a collection of 108 polysomnographies, provided in open access by the Sleep Disorders Centre of the Ospedale Maggiore of Parma, Italy on Physionet [46], [47]. Each polysomnography is provided as an edf file and a txt file with the sleep stage score for each 30s epoch. The edf files of the database include at least "3 EEG channels (F3 or F4, C3 or C4 and O1 or O2, referred to A1 or A2), EOG (2 channels), EMG of the submentalis muscle, bilateral anterior tibial EMG, respiration signals (airflow, abdominal and thoracic effort and SaO2) and EKG. Additional traces include EEG bipolar traces, according to the 10-20 international system (Fp1-F3, F3-C3, C3-P3, P3-O1 and/or Fp2-F4, F4-C4, C4-P4, P4-O2)". The edf format also provides channel labels, filtering, recording duration and other features. It contains recordings of subjects with different pathologies. 22 recordings of subjects with RBD (label: rbd*) and 16 recordings of controls (label n*) were taken into account. The 22 RBD submental EMG channel recordings have the following features: 512Hz sampling frequency except rbd6 which has 256 Hz, microvolt unit of measurement (UoM) except for rbd8 which has mV, 10-100 Hz bandpass filter and 50 Hz Notch applied to the channel, exept for rbd 6 which has 0.3-100 Hz. Files for rbd11 have been excluded because they are the same as rbd10. EMG recordings for the controls do not provide comprehensive information. It is not sure that the EMG signals are all from submentalis channel. For some, the recording settings are not present. Given the type of sampling frequency (should be at least 200Hz for Nyquist) and filtering, many tracks are not suitable for the type of analysis implemented, so they have been excluded from the summary results and from the comparison between RBD and controls an in any case, for these reasons, they have little significance in the analysis. Controls recordings features

are presented in Table 2.1.

	UoM	**Sampling Frequency**	**Applied Filters**	**Comments**
n1	uV	256 Hz	10-100 Hz + N50	
n2	uV	512 Hz	10-100 Hz + N50	
n3	mV	512 Hz	10-100 Hz + N50	
n4	mV	200 Hz	-	LP:100 Hz + N:50 on
n5	uV	512 Hz	10-100 Hz + N50	
n6	uV	128 Hz	-	Not suitable
n7	uV	128 Hz	-	Not suitable
n8	mV	200 Hz	-	LP:100 Hz + N:50 on
n9	uV	128 Hz	-	Not suitable
n10	mV	512 Hz	10-100 Hz + N50	
n11	uV	512 Hz	10-100 Hz + N50	
n12	uV	100 Hz	0.1-100Hz	
n13	-	200 Hz	-	Filters on
n14	-	200 Hz	-	Filters on
n15	-	200 Hz	-	Filters on, amplified amplitude (?)
n16	-	-	-	No EMG

Table 2.1: CAP Database. Controls group features.

	REM (s)
rbd1	3810
rbd10	2490
rbd12	4800
rbd13	6000
rbd14	8940
rbd15	5040
rbd16	3450
rbd17	4170
rbd18	2820
rbd19	4140
rbd2	5460
rbd20	5550
rbd21	3870
rbd22	9000
rbd3	3810
rbd4	8790
rbd5	4920
rbd6	3870
rbd7	1980
rbd8	4320
rbd9	6180

	REM (s)
n1	7170
n10	6540
n11	11430
n13	5490
n14	4950
n15	5940
n2	4530
n3	5640
n4	6270
n5	6960
n8	5940

Table 2.2: CAP Database RBD and CONTROLS subjects. Total REM time recorded.

2.1.2 TURIN

The TURIN Database is a collection of 16 polysomnographic recordings registered at the Sleep Disorders Centre of A.O.U. Molinette in Torino, Italy. The Polysomnographic setup is described in Table 2.4. Polygraph was used. Each polysomnography reported in an EDF file comes with two other txt files: one of them contains the hypnogram, i.e. the sleep stage scored for each 30s-epoch, the other contains a description of the events detected during the night. Both the txt files are filled in by one sleep technologist and revised by another one. The events detected during the night regards episodes of arousals, localised interference in the signal, particular subject's movements or behaviour (e.g. bruxism episodes, leg movements) and cardiac or respiratory events. As for CAP, the edf files provide labels and features of recording of each channel. The total time recorded in REM

stage and the number of events detected to be deleted (reported in the txt files) are shown in table 2.3. The events to be deleted in are due to a recognisable event, which causes changes in the signals, but which are not to be taken into account in the analysis. For this application are: arousals, rhythmic movement and transient muscle activity.

	REM (s)	**N. of Events**
S1	4830	11
S2	2850	57
S3	3570	0
S4	3870	54
S5	3450	39
S6	4320	4
S7	4980	40
S8	2010	26
S9	5730	25
S10	4950	48
S11	3450	10
S12	3480	11
S13	1770	8
S14	1590	0
S15	840	2
S16	4200	30

Table 2.3: TURIN Database. Subjects features.

Channel	Sampling Frequency	Filtering
6 Electroencephalograms	256 Hz	LP:50.00Hz HP:0.30Hz N:50
2 Electrooculograms	256 Hz	LP:30.00Hz HP:0.30Hz N:50
EMG of Mylohyoid muscle	256 Hz	LP:100.00Hz HP:10.00Hz N:50
EMG of Masseter muscle	256 Hz	LP:100.00Hz HP:10.00Hz N:50
2 EMG of right Tibialis anterior	256 Hz	LP:100.00Hz HP:10.00Hz N:50
2 EMG of left Tibialis anterior	256 Hz	LP:100.00Hz HP:10.00Hz N:50
Thermistor	32 Hz	LP:15.00Hz HP:0.05Hz N:0
Air Flow	32 Hz	No
Thoracic Effort	32 Hz	LP:15.00Hz HP:0.10Hz N:0
Abdominal Effort	32 Hz	LP:15.00Hz HP:0.10Hz N:0
SpO2	1 Hz	No
Snoring	32 Hz	LP:100.00Hz HP:10.00Hz N:50
Plethysmography	256 Hz	No
Electrocardiogram	256 Hz	LP:70.00Hz HP:0.30Hz N:50
Position	32 Hz	No
LP: Low Pass, HP: High Pass, N:Notch, EMG: Electromyogram		

Table 2.4: TURIN Database. Polysomnographic Setup.

2.1.3 Vortioxetina Trial

The database consists of 18 polysomnographic recordings of 9 patients, one during the period of administration (ON) of an antidepressant drug (Vortioxetine), the other in the absence of the drug (OFF). The recordings took place at the the Sleep Disorders Centre of A.O.U. Molinette by means of a polygraph. 24 channels were collected with recording characteristics as for the Turin database and shown in table 2.4. All submentalis EMG channel recodings have a sampling frequency of 512Hz, microvolt unit of measurement, 10-100 Hz bandpass filter and 50 Hz Notch filter applied. The total time recorded in REM stage and the number of events detected to be deleted (reported in the txt files) are shown in table 2.6. The participants of these trial do not have a history of RSWA or RBD, but the RSWA quantification on their recordings is relevant because of the antidepressant drugs effect on RSWA. Molinette also provided the manual scoring of Tonic density, Phasic Density Montréal and Phasic Density SINBAR of four recordings. They are reported in Table 2.5.

	Tonic Epochs	Phasic Epochs M	Phasic Epochs S
S2 OFF	13	69	57
S5 ON	0	40	77
S6 OFF	0	18	45
S9 OFF	0	45	59

Table 2.5: Number of epochs scored for each class as resulting from the manual scoring of Tonic and Phasic Epochs with Montréal and SINBAR criteria.

	ON		OFF	
Subj:	REM (s)	N of Events	REM (s)	N of Events
S1	3270	12	3600	18
S2	4140	19	960	102
S3	690	21	750	43
S4	2550	34	2310	31
S5	3150	34	2070	7
S6	960	18	3390	30
S7	3810	33	1440	13
S8	1530	24	990	13
S9	1500	52	2970	87

Table 2.6: Vortioxetina database. Subjects Features.

2.2 RSWA quantification

The aim of this thesis is to analyse the data collected in terms of muscle parameters relating to muscular atonia in an automatic manner, i.e. in the first instance to translate into an algorithm what are currently the visual scoring methods: Montréal and SINBAR. Consequently, this section will describe which parameters were calculated on the recordings for each database and how. Before explaining the method of estimation of the calculated muscle parameters, it is important to point out that the polysomnographies are saved in EDF format and were processed with MATLAB 2021a software. For each one, it was verified that the import was correct, that the file containing the hypnogram and the events was correctly read and corresponded to the polysomnography setting reported in label.

2.2.1 Pre-Processing

A MATLAB function is used to parse data from the edf file and store them in a data structure, with info on the channels and recordings. Another function is used to create a vector from the hypnogram txt file. If the txt file describing the events is also available, another function is needed to read from it the number of the epochs in which there is an event to be deleted. This function scans every line of the txt files searching for events of the type: Arousals, Rhythmic Movement and Transient Muscle Activity. The number of each event affected epoch is saved. The CAP database is already given with MATLAB functions to manage it. The signal of interest and used is the channel recording submental muscle. It is identified through the label and its sampling characteristics are collected. If the signal has a sampling frequency lower than 256 Hz, it is resampled. The unit of measure is changed to microvolt, if different. First of all, the hypnogram is adapted to the sampling characteristics of the channel of interest, i.e., a variable is constructed which contains for each signal sample a label (obtained from the hypnogram one) identifying its sleep stage. If events affected epochs are noted than they are deleted from the signal and from the hypnogram. At this point the signal is prepared for the muscular evaluations so: the average is removed and if the filtering reported in the signal label is different from 10-100Hz, additional filtering is applied as nedeed. If the label do not report any filtering, Power Spectral Density is observed. Extra filter used are:

- High Pass filter at 10Hz realised by a digital Butterworth filter with an order and a cutoff frequency specified 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.

- Band Pass filter 10-100Hz realised by a digital Butterworth filter set as specified before, but with cutoff frequency of 100 Hz added.

- The Notch filter for powerline is obtained through a recursive Notch filter where the centre band frequency (Fc) is set to powerline frequency (50 Hz), the minimum attenuation at frequency Fc is set to 0.01, the bandwidth corresponding to attenuation 0.707 is set to 3 and the sampling interval is set to the time duration of a sample of the signal to be filtered.

CAP rbd subjects recordings were already suitable for the algorithm so no further processing was applied. Controls subjects required more evaluations because of the lack of labels. PSD were used to understand the missing filters and processing was added as needed with the filters specified above. Vortioxetina Database EMG recordings were already suitable for the algorithm so no further processing was applied. Turin Database EMG recordings were suitable for the algorithm, but the

notch filter is not always already applied. No guideline is provided for Notch filters, but some of the recordings present in Turin database where corrupted by power line interference, so a Notch filter is added as specified before.

2.2.2 REM Atonia Index

The function implemented to calculate the RAI follows the improved method presented in 2010. If not present, a notch filter is applied to the recordings, in line with the guidelines on RAI scoring [35]. The RAI function takes as arguments: the signal on which the index is to be calculated, its sampling frequency, the hypnogram and the sleep stage on which it is to be calculated. First the signal is rectified, then the indications in the hypnogram are used to identify the epochs marked as the sleep stage indicated in the function argument. In this case the sleep stage of interest is REM stage, indicated with "5" in the hypnogram. These REM epochs are divided into 1-second sub-epochs, called mini-epochs. The average calculated over the mini-epoch is saved (aa). For each sub-epoch a window of 30 seconds before and 30 seconds after is selected for a total of 61 seconds and the minimum of this is calculated (minWin). At this point the AA (average amplitude of the mini-epoch) is calculated as $AA = aa - minWin$. The total number of miniepochs (TOT), the number of miniepochs with AA $\leq 1\mu$V (AA1) and the number of miniepochs with μV$<$ AA $\leq$2 μV (1AA2) are saved to calculate AI. Indeed AI is easily obtained as:

$$AI = \frac{AA1}{TOT - 1AA2} = \frac{AA1/TOT}{1 - (1AA2)/TOT.}$$

The function also compute the Normalized Distribution Histogram construction. It sorts the AA values in 20 classes. The histogram is constructed by calculating the percentage of miniepochs in each amplitude class. The classes are as specified in the article by Ferri [35] and reported in the previous chapter in section 1.4.1.

2.2.3 Automating Montréal Method

The function implemented to calculate Tonic Density and Phasic density as Montréal Method indicate takes these as arguments: the signal (submentalis EMG) after pre-processing the sampling frequency and the hypnogram. This function has been implemented to directly return the densities.

It processes the arguments to obtain Tonic density as follows:

1. The signal is rectified;
2. The background activity (BKG) is calculated as the 40th percentile of the N3 epochs only (marked as 3);

3. Each 30-seconds REM epoch (marked as 5) is examined:
    - A sample is considered to be *increased activity* if its amplitude is twice as large as the background or if it exceeds 10 microvolts;
    - The epoch is scored as *tonic* if more than 50% of the samples are increased activity;
4. Tonic Density is computed as the percentage of tonic epochs out of total REM epochs.

The function processes the arguments to obtain Phasic Density as follows:

1. The signal is rectified;
2. The background activity (BKG) is calculated as the 40 percentile of the N3 epochs only (marked as 3);
3. The REM epochs only are taken into account and are examined:
    - The position (sample number) of all samples with an amplitude greater than four times the background activity (supra- threshold) is saved;
    - Activity bursts are identified by checking when the position of supra-threshold samples is not adjacent. Neighbouring supra-threshold samples are considered to belong to the same burst. Distant supra-threshold samples are considered to belong to two different bursts. The limiting distance is considered to be 3 samples: 3 or more samples far apart means different bursts;
    - Once the activity bursts have been identified as indicated above, their duration is calculated;
    - Bursts with duration between 0.1 and 10 seconds were considered. For each of them the duration is stored;
    - The number of 2-s epochs contained in their total duration (sum of all the bursts' duration) is counted and taken into account as phasic scored epochs;
4. The phasic density is calculated as the number of phasic scored epochs out of total REM epochs. It is then multiplied for 100 to have the percentage.

2.2.4 Automating SINBAR Method

The function implemented to calculate Tonic Density, Phasic density and Any density as SINBAR Method indicate takes these as arguments: the signal (submentalis EMG), the sampling frequency and the hypnogram. This returns the scoring

result for each epoch, not directly calculating the density, which is calculated retrospectively. Scoring involves creating a vector of the length of the number of epochs (either 30 seconds or 3 seconds epochs) and indicating for each:

- 0 if is not scored;
- 1 if it is tonic/phasic;
- 2 if it is NOT tonic/phasic.

The function processes the arguments to obtain Tonic Density in a different way from the other function used for the Montréal method, however the criteria for this indicator are the same and the results must match and actually match. Both implementations are presented for illustrative purposes, but only one indicator will be shown in the results, corresponding to the tonic density parameter calculated on epochs of 30 seconds. The function presented here gives a vector containing the tonic scoring of each REM 30s-epochs (ScoringT30) and a vector containing the phasic scoring of each REM 3s-epochs (ScoringP3) as an output. It processes the arguments as follows:

1. The signal is rectified;
2. The background activity (BKG) is calculated as the 40th percentile of the N3 epochs only (marked as 3);
3. The vector containing the tonic scoring of each 30s-epochs (ScoringT30) is initialised (length of the number of REM epochs and value 0) Same for the vector containing the phasic scoring of 3s-epochs (ScoringP3);
4. 30-seconds REM epochs (marked as 5) are isolated and linked. Each epoch is considered separately;
5. Tonic Scoring of the epoch is done as follows:
   (a) A sample is considered to be increased activity if its amplitude is twice as large as the background or if it exceeds 10 microvolts;
   (b) If more than 50% of the samples of the epoch are increased activity then the element of the vector ScoringT30 corresponding to the epoch under consideration is set to 1. If not then to 2;
6. Tonic Density is easily calculated at the end of the process from ScoringT30 as the ratio between the number of "1" in the vector and the total length of the vector (corresponding to the total number of REM epochs). It is then multiplied for 100 to have the percentage;

7. Phasic Scoring of the epoch is done as follows:
   (a) The 30s-epoch is divided into ten 3s-epochs.
   (b) For each of them the position (sample number) of all samples with an amplitude greater than two times the background activity (supra- threshold) is saved;
   (c) Activity bursts are identified by checking when the position of supra-threshold samples is not adjacent. That is, neighbouring supra-threshold samples are considered to belong to the same burst. Distant supra-threshold samples are considered to belong to two different bursts. The limiting distance is considered to be 3 samples: 3 or more samples far apart means different bursts;
   (d) Once the activity bursts have been identified as indicated, their duration is calculated and stored;
   (e) If there is at least a burst with duration between 0.1 and 5 seconds then the element of the vector ScoringP3 corresponding to the epoch under consideration is set to 1. If not then to 2;
8. From the total duration of all the bursts in each miniepoch, the phasic activities longer than 5 seconds are found and counted (as consecutive epochs of phasic activity close to 3 seconds) so that they can be subtracted from the number of epochs scored as 1;
9. Phasic Density is easily calculated at the end of the process from ScoringP3 as the ratio between the number of "1" in the vector and the total length of the vector (corresponding to the total number of REM epochs). It is then multiplied for 100 to have the percentage;
10. Any Chin Density is calculated as the number of 3s-epochs scores as tonic or as phasic (or both together) out of the total REM epochs obtained from the length of ScoringP3 as before. It is then multiplied for 100 to have the percentage.

The calculation of phasic activity implemented in this work, as can be seen, varies substantially in implementation from the Montréal method one. As a matter of fact here one looks for phasic activity in the sub-epoch while in the previous case there was no pre-division. This means that the bursts detected here can never be longer than 3 seconds. Since the searched bursts have a minimum duration of 0.1 second in order to score the entire 3s-epoch as phasic this should in theory not change the count for bursts of less than 5s duration covering different epochs. However, if the burst has a duration of more than 5s, since the epochs are analysed separately, the algorithm cannot actually detect it. For this reason the eighth step

in the calculation of the phasic scoring is added. In these databases the FDS EMG signal was not recorded therefore it was not possible to score the phasic activation of this muscle and obtain the "Chin+FDS Density".

2.3 Background Activity Evaluation

The key amplitude threshold of visual methods is the background muscle activity (BKG). This is defined as the minimum muscle activity found in slow-wave sleep [16]. It allows not having to establish a single amplitude threshold for all patients, but to adapt the value to the patient's maximum resting muscle tone. Indeed, it is possible for different subjects to maintain a different residual muscle tone even in non-pathological conditions. This threshold is established visually by observing the rectified signal. The algorithm must translate this observation into mathematical terms. The method employed in this work is the 40th percentile of the rectified N3 electromyogram, because it provides background values that are much closer to those visually perceived than the mathematical minimum. This threshold, however, is not the only one in this method, the elevated muscle activity is also indicated by a threshold (it is the activity that exceeds 2/4 times that of BKG) and the critical threshold that distinguishes normal from pathological density values is yet another threshold. These 3 thresholds influence each other; e.g, if the BKG value is lowered keeping the same definition of sustained activity, pathological densities will be represented by a higher density. Following the guidelines, the density values of healthy subjects are normally very low, even around 0%. Physiologically they are unlikely to be high. This makes this metric not fully exploitable in the description of the phenomenon and makes the choice of background activity more difficult. Indeed, a low threshold (e.g., 25 percentile) is always patient specific, but would include many more samples in the analysis and allow a finer description (e.g., exploiting the whole 0-100% density scale). However, a low threshold includes background noise as well as cross talk from other channels and makes it impossible to distinguish the source of the amplitude increase. Therefore it is also important to rely on medical information such as the fact that the muscle activity of interest exceeds the baseline by 2/4 times. For these reasons, an effective translation of the visual information into mathematical terms is crucial in the faithful automation of this method, as it is being, as is maintaining consistency between thresholds. To show the effect of the BKG threshold changes, RSWA scoring results with different BKG estimations are reported:

- BKG calculated as the mean of the rectified N3 electrormyogram;
- BKG calculated as the median of the rectified N3 electrormyogram;
- BKG calculated as the 25 percentile of the rectified N3 electrormyogram.

2.4 EKG Artifact Removal

Often there is a clearly visible EKG artefact in the submental EMG recording. Indeed, the power of the EKG signal is much higher than that of the electromyographic signal and the two signals partly overlap in bandwidth. Under certain conditions, whether setup or subject-specific, it can happen that the EKG has a considerable amplitude also in the EMG recording. When parameters based on amplitude are evaluated on this trace, this artefact definitely represents a disturbance.

In electrical potential detection using surface electrodes on the skin, the electrical behaviour of the heart is, under standard sampling conditions, displayed in a characteristic waveform called the PQRST complex. The complex is shown in Figure 2.1. Each beat of the heart corresponds to a train of electrical impulses that allow asynchronous contraction of the atria and ventricles through complex innervation. The contraction of the walls of the ventricle is the most demanding and for this reason the polarisation of the ventricles has the greatest amplitude in the signal. This produces the QRS complex in the tracing, in which the R wave stands out in amplitude. The shape of the complex, however, depends on the position of the electrodes (as well as the quality of the recording). For this reason the wave shape is not maintained on the other surface pick-up channels. However, even if deformed, it is usually possible to see the R, RS or QRS complex on the other recording channels. If it cannot be eliminated by filtering, it is possible that the R-wave, representing such an intense electrical polarisation, will stand out on the trace. This often occurs in EMG channels.

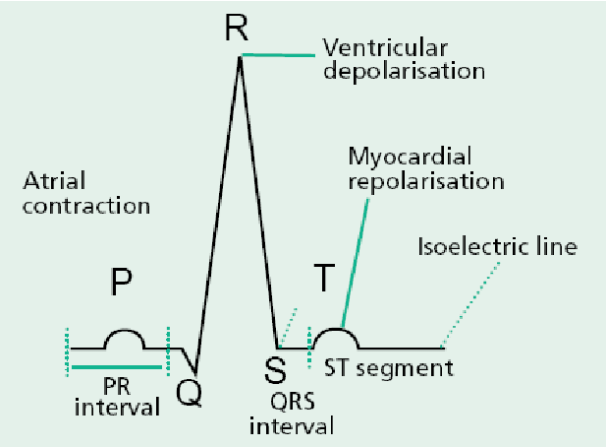

Figure 2.1: PQRST Complex wave [48].

In this work a method of R peak isolation is presented. It was developed exploiting the TURIN database, which features many traces affected by a clearly

visible EKG artifact on the EMG channel. An example is shown in Figure2.2, where the R peak exceeds the muscular activity in amplitude.

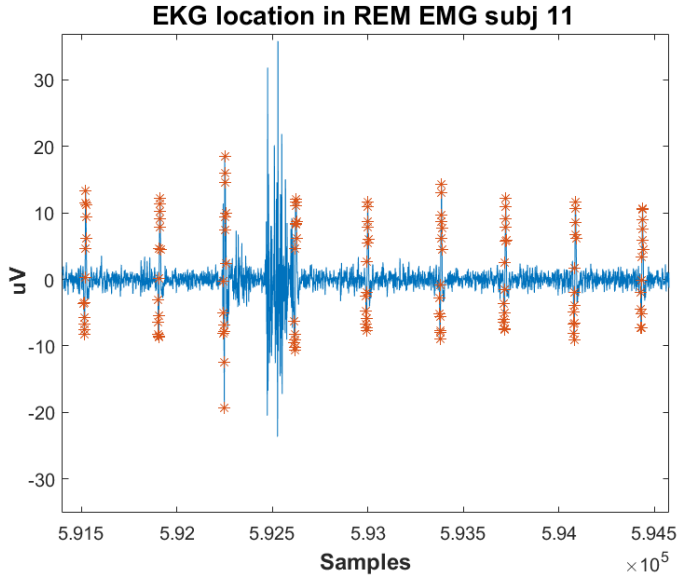

Figure 2.2: Around 12 s of chin EMG in subj 11. In orange samples marked as EKG artefact.

This method uses the EKG channel to identify R peaks, as a matter of fact the electrocardiographic signal is usually well recorded and clean (given its characteristics). In summary, the algorithm works in 3 main steps:

1. The R peaks in the EKG trace are identified temporally;
2. The delay between the appearance of the R peak in the EKG trace and in the EMG trace of interest (submental in this case) is estimated;
3. A number of samples around the R peak covering its waveform is estimated.

At this point the EKG artefact present in the EMG trace is localised. It can be flagged or directly eliminated from the overall trace. In this case we tried to eliminate it to see how the values of the muscle parameters are affected by this artefact.

To identify the R peaks in the EKG trace the MATLAB function findpeaks is exploited. It is used to find (in the REM EKG trace) peaks with an amplitude at least of "minH" amplitude and distant more than "minD" samples. MinD is set by default at 1/3 seconds so fs/3 samples. This means that it not possible to detect more than 3 beats per second, corresponding to 180 bpm. This threshold was used to help the algorithm to identify R peaks in presence of noise, but it

is also physiologic, indeed, it is very unlikely that the heart rate will reach 180 bpm during the night, however possible extrasystoles are not caught (conservative choice). MinH is set by default to 1 mV, but because of the fact that not all the recording set ups produce the same amplitudes, a threshold resetting is also foreseen in case the 97th percentile of the signal is less than minH (regardless of the sign). This threshold was deduced from the data. It has also been taken into account that the track can be recorded with the polarity reversed. This means that the findpeaks function was usedto find peaks greater than minH both on the signal and on the signal changed sign. The algorithm is able to figure out by itself whether the R peak is in the positive or negative part of the signal even if the polarity of the EKG trace changes overnight, as found in some recordings in our dataset. One of the recordings in Turin database showed an EKG with polarity inversion and not standard EKG channel recording, a portion of EKG is showed in Figure 2.3.

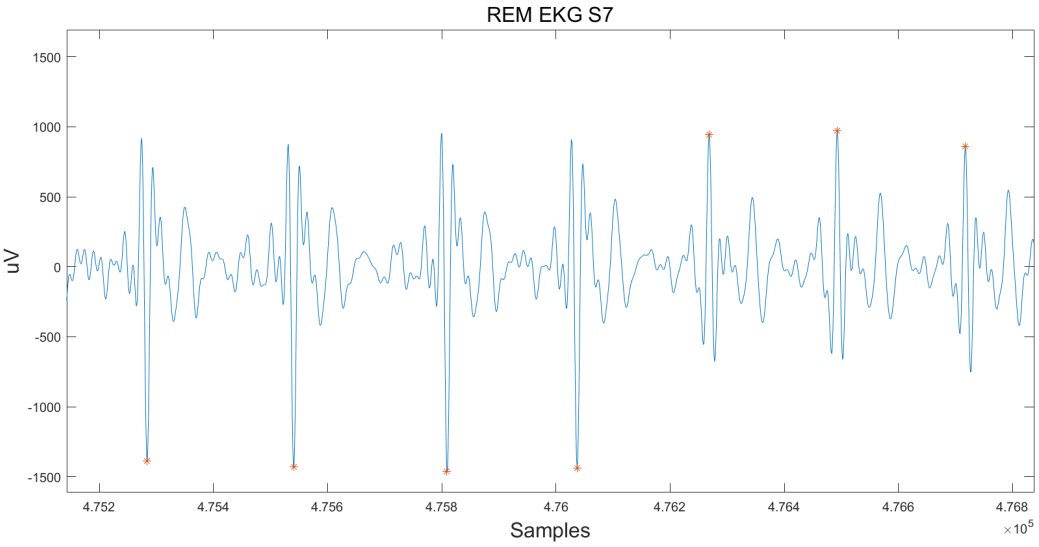

Figure 2.3: R peak detection in EKG tracing with sign inversion.

as a matter of fact, once the algorithm has found (position and amplitude are saved) the peaks that meet the above criteria, for each of these it checks that the peak of the opposite polarity, if any, is smaller. If this is not the case, the peak is replaced by the one of greater amplitude. This process guarantees the correct identification of the R peak for this database. At this point the corresponding temporal position on the EMG traces is saved. To do that the delay between the appearance of the R peak in the ECG trace and that in the EMG trace is estimated. For the electrode configuration of the TURIN database, the delay was visually estimated between 4 and 6 samples and set to 5 samples. An example of visual

estimation is shown in Figure 2.4.

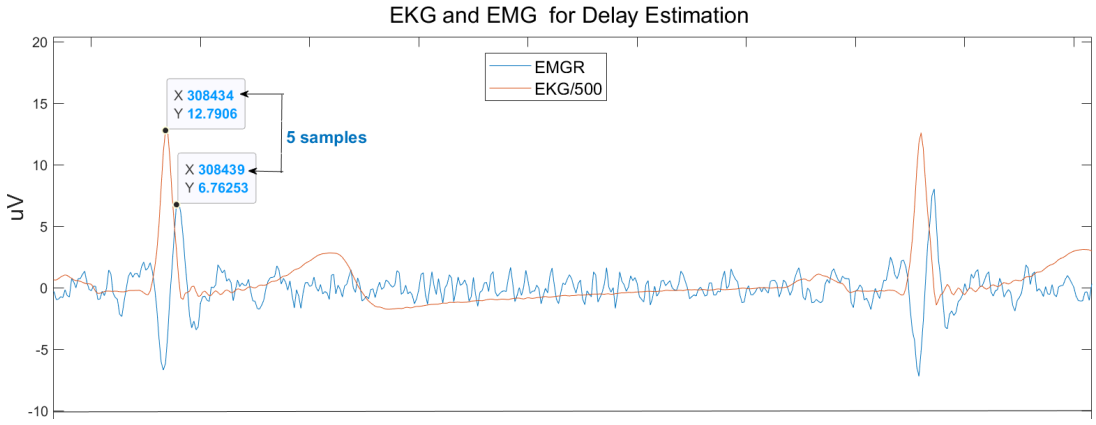

Figure 2.4: R peak Delay Estimation.

This means that each R-peak position found in the EKG is increased by 5. In addition, it is estimated how many samples around the R peak are part of the EKG artefact. This can vary from patient to patient, for the TURIN database it was seen that the most visible complex in the EMG tracing is the QS complex which in most cases is between nine samples before the R peak and four samples after, corresponding to a duration of about 55 milliseconds (256Hz sampling frequency). In this case, a conservative choice was made, i.e. as few samples as possible were marked as corrupted, so that only the most prominent parts of the peak were removed. Examples of EMG waveform marked as EKG artefact are shown in Figure 2.5 .

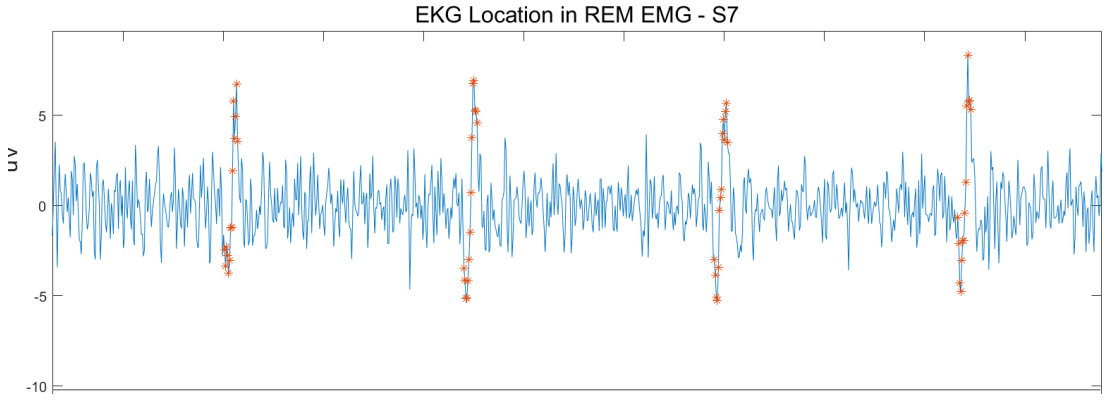

Figure 2.5: EMG Samples Marked as EKG Artefact.

In reality some patients also have the S peak quite visible, for these cases it is possible to set the parameters individually after viewing the trace. This also

applies to the other thresholds. In order to have a comparable result, the same thresholds were used in the results for all patients:

- minH = 1 mV or 97th percentile of REM EKG,
- minD = fs/3,
- Delay= 5 samples,
- Artifact duration: 14 samples, 9 before R location and 4 after.

The results present the scoring of the previously described muscle parameters carried out on the submental EMG recordings after all samples marked as corrupted were removed. The percentage of samples removed is also reported. The limitations of this method are identified as follows:

- Objective quantification of when the EKG removal is needed and is missing.
- The QRS complex in the EMG can vary in shape and and be subject to jitter, i.e., the delay between the R peaks in the EMG and EKG is not fixed. This means that it is not possible to be sure about the number of samples to be marked as artifact around the R-peak. However, as long as the aim is to identify the most prominent peak, this problem has a limited effect.
- The R peak identification is based on EKG channel. If the EKG the tracing presents amplitude jumps or heavy distortions, the R peak identification can not properly work.

Chapter 3

Results

3.1 Atonia Index Scoring

In the subsequent subsections the results of REM Atonia Index computation are reported in details for each database. The AI value is adimensional, in literature values under 0.8 are considered indicative of RBD.

3.1.1 CAP Database

Atonia index scoring for RBD subjects of the CAP Database are shown in Table 3.1. The AI value is adimensional, in literature values under 0.8 are considered indicative of RBD. The percentage of subjects that scored an AI in the intervals: AI>0.9, AI<0.8 and 0.8<AI<0.9 are at the bottom of the Table. Only one subject has an AI grater than 0.8. Anyway there is no event location for the CAP database, so there is no evidence that the overall increased amplitude is uniquely due to the lost atonia. The Atonia Index computed for Controls subjects in CAP Database are shown in Table 3.2; 37.5 % of the subjects showed an AI>0.8.

	AI
rbd1	0.0046
rbd10	0.753
rbd12	0.491
rbd13	0.0035
rbd14	0.218
rbd15	0.0434
rbd16	0.0258
rbd17	0.992
rbd18	0
rbd19	0.129
rbd2	0.193
rbd20	0.615
rbd21	0.643
rbd22	0.11
rbd3	0
rbd4	0.0361
rbd5	0.0553
rbd6	0
rbd7	0
rbd8	0.456
rbd9	0
MEAN	0.2271
STD	0.3024
P(AI>0.9)	4.3 %
P(0.8<AI<0.9	0 %
P(AI<0.8)	92.2 %

Table 3.1: CAP Database RBD subjects. REM Atonia Index Scoring.

	RAI
n1	0.955
n10	0.882
n11	0.377
n2	0.344
n3	0.909
n4	0
n5	0.653
n8	0.0078
MEAN	0.516
STD	0.39
P(AI>0.9)	25 %
P(0.8<AI<0.9)	12.5 %
P(AI<0.8)	62.5 %

Table 3.2: CAP Database. Controls REM Atonia Index Scoring.

In summary, using this parameter 92.2% out of the rbd subjects in CAP database showed AI under 0.8, but the values too close to zero are probably due to different recordings setup or lack of information. Indeed also between controls AI values are very low: only 37.5 % of the subject showed an AI>0.8. However it must be considered that controls' subjects recordings present with incomplete documentation. As a matter of fact, n13, n14 and n15 show very high amplitudes and seem to be recorded in US, given the powerline notch at 60 Hz. It is not possible to establish if there was an amplification applied and how great, therefore these subjects are excluded from this analysis that uses a fixed amplitude threshold. Normalized Distribution Histogram for all subjects RBD is shown in Figure 3.1. It is intresting to notice that RBD histogram respect in shape the one presented in Ferri article for iRBD [35], showing the first bin lower than the second.

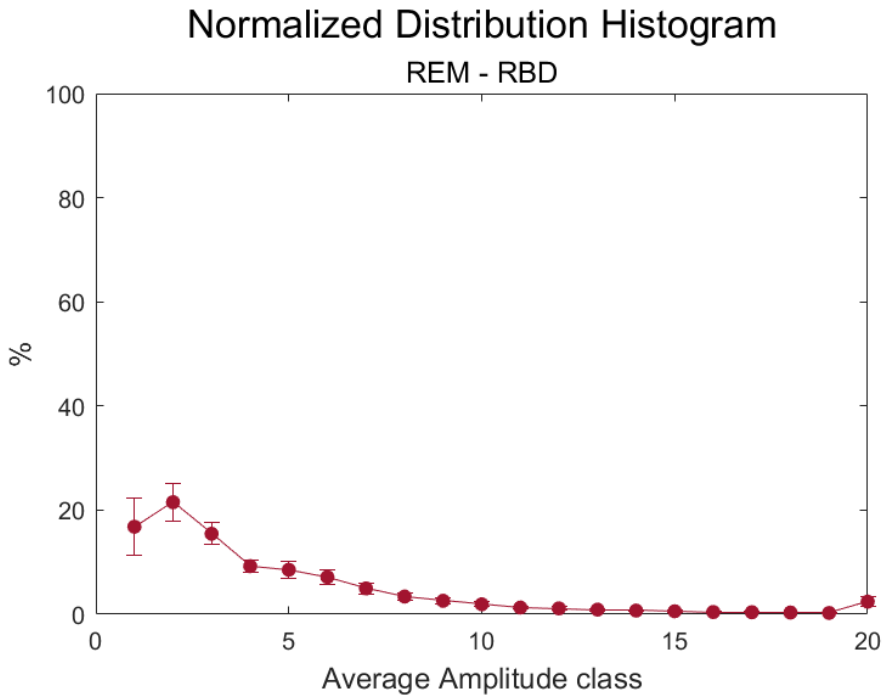

Figure 3.1: CAP Database - RBD. Normalized Distribution Histogram of REM Chin EMG Averaged Amplitude of all subjects, with Standard Error (SE).

3.1.2 TURIN Database

The subjects in this database present with RBD-like manifestation (severity is not known). Results are shown in Table 3.3. Only 50% of the subjects actually showed an AI<0.8. Although the recordings are recent and conducted in a specialised centre following the guidelines, it is clear that amplitude-based methods need a more accurate set up description or specific data visualization protocol in order to produce reliable results.

	AI
S1	0.762
S2	0.956
S3	0.937
S4	0.108
S5	0.946
S6	0.953
S7	0.245
S8	0.582
S9	0.96
S10	0.64
S11	0.837
S12	0.972
S13	0.0059
S14	0.983
S15	0
S16	0.58
MEAN	0.6542
STD	0.3668
P(AI>0.9)	43.75 %
P(0.8<AI<0.9)	6.25 %
P(AI<0.8)	50 %

Table 3.3: TURIN Database. Atonia Index Scoring.

3.1.3 Vortioxetina Database

The Results are shown in Table 3.4. The Vortioxetina database contains PSG recordings of subjects before (OFF) and after (ON) the use of an antidepressant drug. Antidepressants are supposed to affect the atonia, subjects after using it should present lower AI and higher densities. The effect of the antidepressant drug on the RAI scoring is shown in Figure 3.2.

The Normalized Distribution Histogram was also created by sorting the amplitude values in 20 classes. The classes are of the type: 1 μV< AA $\leq$ 2 μV, 2 μV< AA $\leq$ 3 μV etc. Where AA stays for average amplitude of the 1s-epoch. They can be built for each sleep stage and were used in the development of RAI. They can indicate whether the Database is suitable for RAI or not. Histograms obtained from Vortioxetina database regarding REM chin EMG are shown in Figure 3.3 for the first recording and Figure 3.4 for the second.

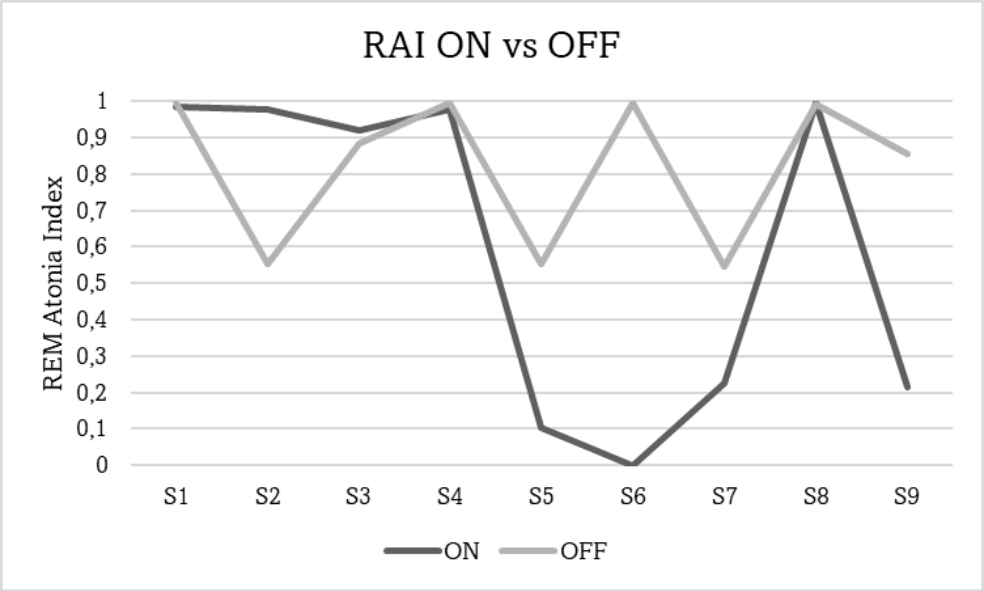

Figure 3.2: Vortioxetina Database. RAI scoring ON vs OFF.

	ON	**OFF**
Subj	**AI**	**AI**
S1	0,9862	0,9972
S2	0,9776	0,5517
S3	0,9216	0,8853
S4	0,9764	0,9944
S5	0,104	0,5531
S6	0	0,9949
S7	0,2258	0,5444
S8	0,996	0,9929
S9	0,2154	0,8557
MEAN	0,6003	0,8188
STD	0,4455	0,2083
P(AI>0.9)	56 %	44 %
P(0.8<AI<0.9)	0 %	22 %
P(AI<0.8)	44 %	33 %

Table 3.4: Vortioxetina database. Atonia Index Scoring.

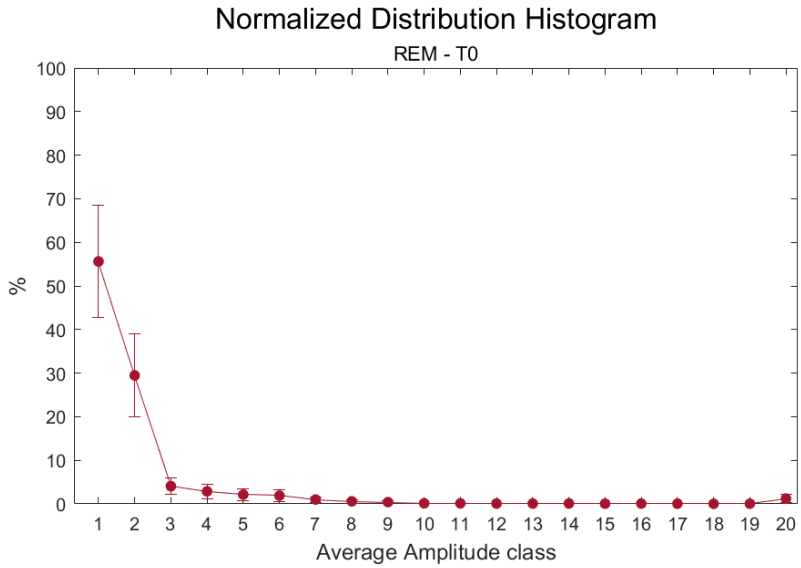

Figure 3.3: Vortioxetina Database. Normalized Distribution Histogram of REM Chin EMG Averaged Amplitude in T0 of all subjects (with SE)

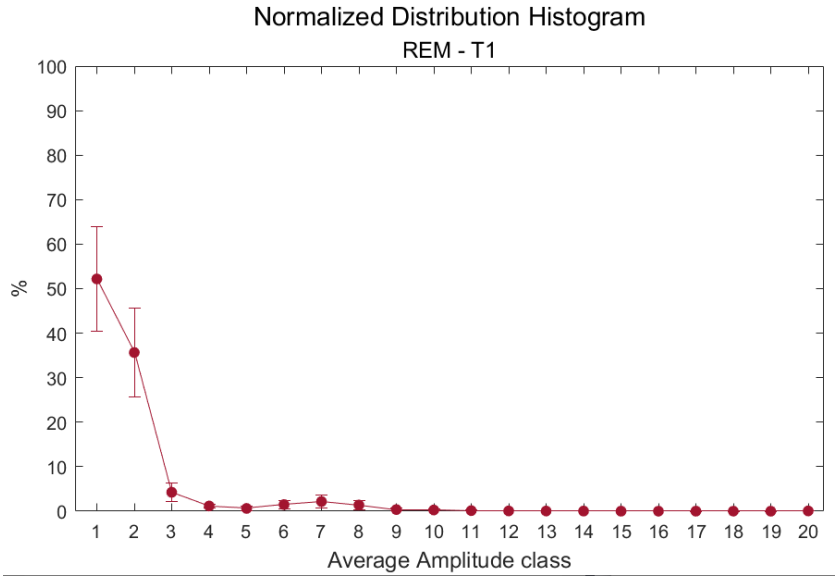

Figure 3.4: Vortioxetina Database. Normalized Distribution Histogram of REM Chin EMG Averaged Amplitude in T1 of all subjects (with SE).

3.2 RSWA Scoring

Tonic Density and Phasic Density are the percentage of tonic and phasic epochs out of the total REM epochs (artefacts excluded). They can be scored with Montréal or SINBAR methods [37]. Both methods are based on amplitude thresholds but these threshold are dependent on the Background muscular activity (BKG) of the subject that is estimated specifically on the patient's recording. The BKG is estimated as the 40th percentile of chin REM EMG recording. Here the results of these parameters estimation with the method described in the previous chapter are reported. It is important to notice that the algorithm used closely follows the guidelines, in the attempt of translating them in automatic form. This has important limitations.

Tonic Density is considered as pathological when is greater than 30 % (Montréal and SINBAR). Phasic Density is considered to be pathological when is grater than 15% for Montréal method or greater than 16.3% for SINBAR method. Chin Any Density is only described in the SINBAR method and it is considered pathological when greater than 18%.

3.2.1 CAP Database

In the CAP Database, 15 rbd subjects out of 21 showed pathological densities. Rbd 1, 5, 6, 7, 9 and 13 showed a very high estimated background activity, which could be due to artifacts or noise on the channel. Rbd 7, 6, 16 showed high densities anyway, while the others are all under pathological threshold. This could mean that the N3 stage is more affected by noise than REM or that the subject's resting tone in higher. The same subjects showed AI scoring close to 0, confirming the high amplitude of the trace and the susceptibility to noise of ampltude-based methods. Rbd 5 and rbd 18 showed RAI around 0 (complete loss of atonia), but under pathological threshold densities. This could mean that the channel has a higher amplitude than expected, but no strong corruption, so that RAI is influenced, in contrast to the densities. Complete results are shown in Table 3.5. The CAP database Control subjects are referred to as n*. In this computation n13, 14 and 15 are considered because an amplitude amplification, if any, does not affect the method since it is based on the BKG threshold and not on an absolute one. As expected they show high BKG values. Complete results are shown in table 3.6.

	BKG (μV)	**TD**	**PD M**	**PD S**	**AD S**
rbd1	4.8220	0	0.052	5.9	5.9
rbd10	1.2210	1.2	0.32	8.1	8.4
rbd12	0.8242	15	5.2	40	43
rbd13	1.7090	76	8	77	83
rbd14	0.6715	53	4	65	73
rbd15	2.1980	21	8.8	31	34
rbd16	3.4800	6.1	0.75	22	23
rbd17	0.3052	0	0.43	5.9	5.9
rbd18	2.5030	0	0.071	8.5	8.5
rbd19	1.7710	11	1.1	23	25
rbd2	1.8620	38	5.7	49	55
rbd20	0.7325	30	1.9	37	40
rbd21	0.7473	26	4.9	36	42
rbd22	2.4110	11	1.8	17	19
rbd3	2.6860	29	0.94	33	40
rbd4	0.8851	47	1.8	39	57
rbd5	5.4950	2.4	0.12	8.2	8.9
rbd6	6.5020	21	4.2	40	42
rbd7	3.2670	3	2.3	40	41
rbd8	0.8507	19	2.2	43	45
rbd9	4.5780	0	0.065	5.2	5.2
MEAN	2.3582	19.5095	2.6023	30.1810	33.5619
STD	1.76	20.52	2.64	19.89	22.48

Table 3.5: CAP Database RBD subjects. RSWA Scoring. TD: Tonic Density, PD: Phasic Density, AD: Any Density, M: Montréal Method, S: SINBAR Method. Densities are measured in percentage.

	BKG (μV)	TD	PD M	PD S	AD S
n1	0.6466	3.8	0.8900	11	12
n10	0.4861	19	2.3000	26	30
n11	1.099	45	14	39	51
n13	6.184	6.6	2.8	17	18
n14	7.896	25	16	23	33
n15	16.26	19	1.4	16	24
n2	2.007	31	16	32	34
n3	0.4591	31	3.5	27	32
n4	0.9821	3.8	1.5	31	31
n5	0.7936	17	1.4	19	23
n8	0.993	1.5	0.61	8.1	8.2
MEAN	3.437	18.4	5.5	22.6	26.9
STD	4.9368	13.9	6.4	9.4	11.8

Table 3.6: CAP Database Controls subjects. RSWA Scoring. TD: Tonic Density, PD: Phasic Density, AD: Any Density, M: Montréal Method, S: SINBAR Method.

3.2.2 TURIN Database

The SINBAR and Montréal algorithms provide the results shown in Table 3.7. Nine out 16 subjects showed pathological values. The BKG estimations are very high for subjects 4 and 15. Subject 15 showed high densities anyway.

	BKG (μV)	TD	PD M	PD S	AD S
S1	1.345	0	0.5	6.8	6.8
S2	0.9801	0	0.35	11	11
S3	0.569	5.9	2.6	38	39
S4	8.3	0	0.1	3.1	3.1
S5	0.6817	0	0.93	27	27
S6	1.049	0	0.32	5.6	5.6
S7	1.288	3	1.9	35	35
S8	0.8481	4.5	2.7	50	51
S9	2.46	0	0.17	3.4	3.4
S10	0.6257	23	13	55	62
S11	0.6452	5.2	3.4	70	71
S12	0.6767	0.86	1	13	13
S13	2.8	3.4	1	24	24
S14	1.387	0	0.13	3.6	3.6
S15	6.627	3.6	0.24	24	25
S16	0.8417	1.4	1.3	37	37
MEAN	1.9453	3.1788	1.8525	25.4063	26.0938
STD	2.27	5.69	3.15	20.6851	21.6619

Table 3.7: TURIN Database. RSWA scoring. TD: Tonic Density, PD: Phasic Density, AD: Any Density, M: Montréal Method, S: SINBAR Method.

3.2.3 Vortioxetina Database

Complete computed results on the Vortioxetina database are shown in Table 3.8 and Table 3.9. The subjects' expected RSWA score is not known, but they are not diagnosed RBD patients. Moreover ON densities are supposed to be higher than OFF ones, since Vortioxetina is supposed to worsen the motor symptoms. This trial did not provide evidence of this effect. Subjects 5 and 7 showed pathological densities in both recordings with plausible values of BKG. ECG artefact is reported by sleep technologists for subject 7, but no abnormality for subject 5. Subjects 1, 4, 5, 6 showed higher values of Any Densities in ON recordings. Subjects 1, 2, 3, 4, 8 showed higher values of Phasic Densities computed with Montréal method in ON. Regarding the comparison with manual scoring result it is possible to notice the great importance of proper recording. Indeed, all the recordings except S6 have high BKG and high amplitudes that results in high densities scoring not related to the manual scoring. Results comparison in shown in Table 3.10. To better appreciate the data in summary form, the calculated (On and Off vortioxetine) metrics are presented in Figure 3.5.

In most of the cases it is easy to explain where computed values come from. While a sleep technologist knows witch which part of the recording it is not significant, the algorithm takes everything into account. As an example REM chin EMG in REM and N3 stages of subject 5 in T1 (OFF Vortioxetina) are shown in Figure 3.6. It is clear that the first part of the EMG recording is not following the classic amplitude values for this channel, as well as N3 that shows many amplitude jumps. The high amplitude of the first part of REM EMG explains the high values of TD and PD found (TD = 32%, PD M = 22%, PD S = 30%).

	BKG (μV)	**TD**	**PD M**	**PD S**	**AD S**
S1	1.7700	0	0.056	0.58	0.58
S2	2.8690	0	0	1.6	1.6
S3	1.6480	0	0.27	11	11
S4	0.9759	0	0.087	2.7	2.7
S5	0.9153	32	22	30	43
S6	0.8541	0	0.12	1.8	1.8
S7	0.7942	29	18	48	54
S8	0.7335	0	0.2	13	13
S9	0.9417	8.1000	4.3	12	16
MEAN	1.3864	9.6778	2.1926	16.1867	17.0756
STD	0.6615	17.3338	3.3093	20.5984	21.3900

Table 3.8: Vortioxetina Database. RSWA Scorings OFF. TD: Tonic Density, PD: Phasic Density, AD: Any Density, M: Montréal Method, S: SINBAR Method. The unit of densities is the percentage.

	BKG (μV)	TD	PD M	PD S	AD S
S1	2.748	0	0.12	1.5	1.5
S2	2.932	0	0.29	1.1	1.1
S3	2.016	0	0.29	5.2	5.2
S4	1.955	0	0.16	3.4	3.4
S5	1.282	45	8.8	52	54
S6	1.404	0	0	9.7	9.7
S7	1.403	34	5.9	51	53
S8	0.611	0	0.26	6.7	6.7
S9	1.708	0	0.13	2.8	2.8
MEAN	1.676	6.7778	4.5833	12.0444	14.1556
STD	0.828	13.47	8.798	16.152	19.845

Table 3.9: Vortioxetina Database. RSWA Scorings ON. TD: Tonic Density, PD: Phasic Density, AD: Any Density, M: Montréal Method, S: SINBAR Method. The unit of densities is the percentage.

	Manual			Automatic		
	TD	PD M	PD S	TD	PD M	PD S
S2 OFF	40.6	14.3	17.8	0	0	1.6
S5 ON	0	2.54	7.33	45	8.8	52
S6 OFF	0	1.062	3.98	0	0.12	1.8
S9 OFF	0	3.03	5.96	8.1	4.3	12

Table 3.10: Manual vs Automatic scoring of Tonic and Phasic Epochs with Montréal and SINBAR criteria.

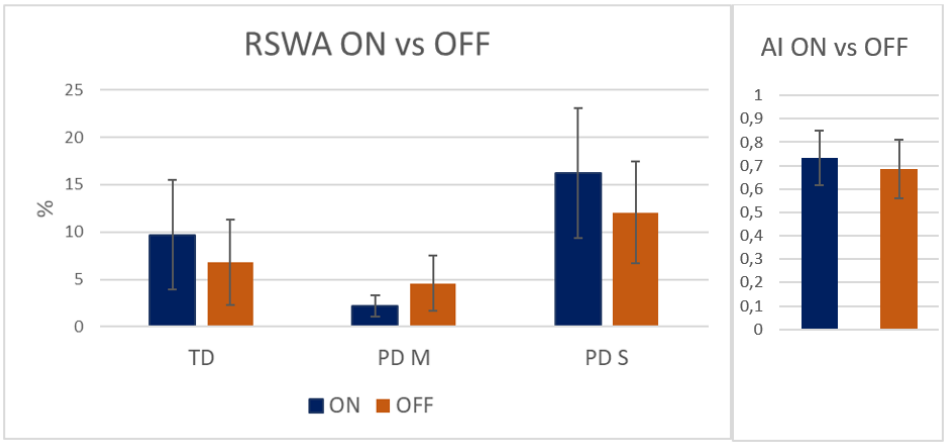

Figure 3.5: AI and Densities summary results ON and OFF Vortioxetina.

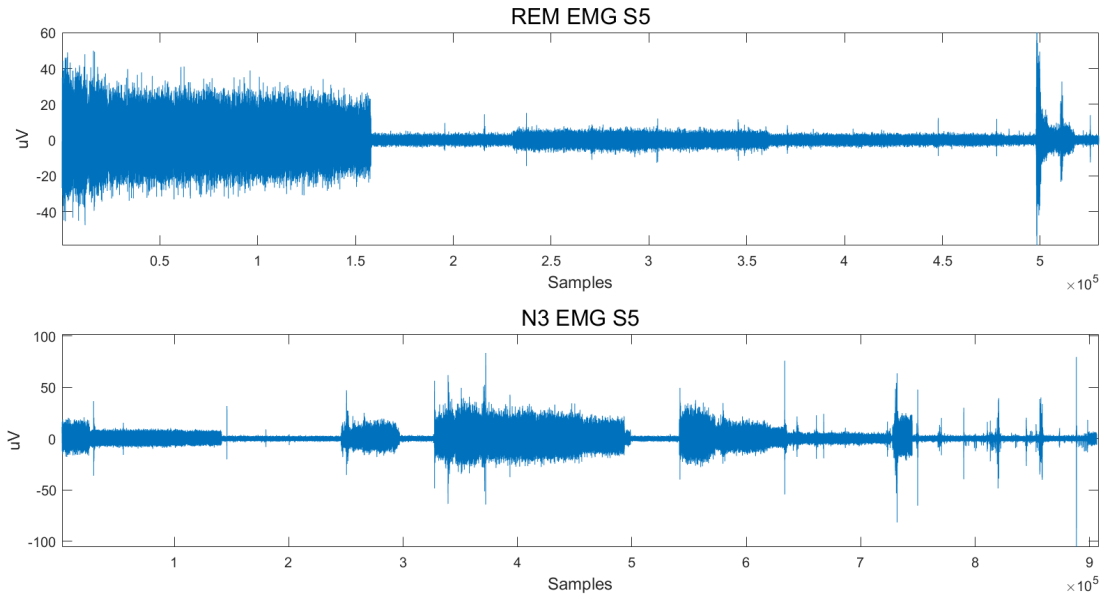

Figure 3.6: Vortioxetina Database. Chin EMG of subject 5 OFF in REM and N3 Sleep Stage.

3.3 BKG Activity Evaluation

Scoring of Tonic Density, Phasic Density as Montréal, Phasic Density as SINBAR and Any Density as a function of the Background activity estimation are shown in the Tables 3.11, 3.12 and 3.13. BKG1 refers to the estimation of the BKG as

the mean of the N3 submental EMG, BKG2 is estimated as the median of the N3 submental EMG, while BKG3 as the 25 percentile of the N3 submental EMG. It is interesting to see that the changing of the BKG does not change the scoring linearly. Taking as an example Tonic Densities for the sixteen subjects, it is important to notice that subjects: 1, 2, 4, 6, 9, 12, 14 present very similar TD values with all three BKG. Tonic Density scoring as a function of the four different BKG is shown in Figure 3.7.

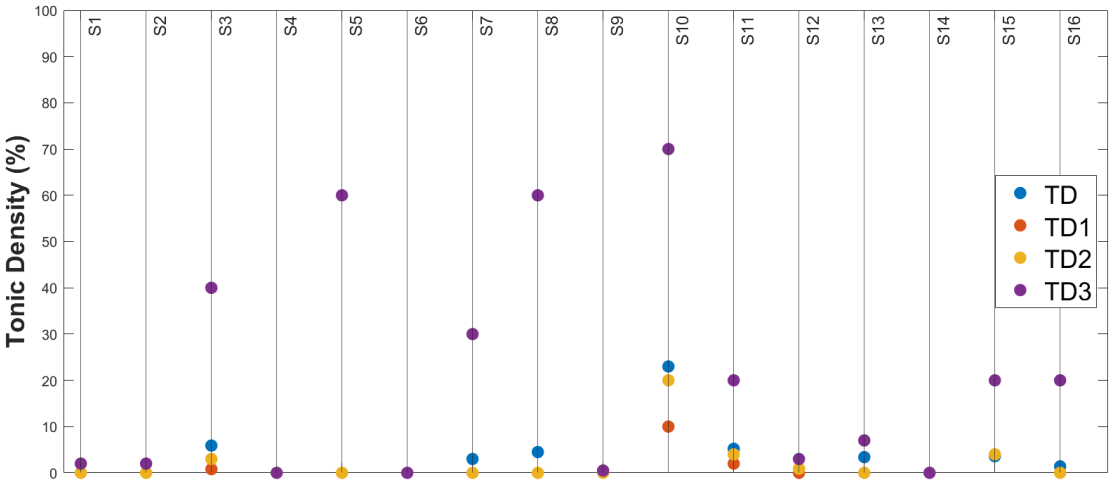

Figure 3.7: Turin Database. Tonic Density as a function of the BKG estimation. TD is calculated as in the algorithm, T2 with BKG2, TD3 with BKG3.

Because of the fact that 40 percentile, the median of a distribution and in some cases also the mean are closer than the 25 percentile can be that TD1, TD2 and TD are closer than TD and TD3. That is generally observed and Tonic Densities scoring with median and mean are superimposed except for subjects 3,10,11. As a matter of fact, for all the subjects except 10, TD scoring remain close and under the diagnostic threshold for TD in all three cases. Without reference scoring of densities it is impossible to establish an optimized value of the background but is also possible to notice in Figure 3.7 that with background around the mean or median of the distribution represented by the samples of the submental EMG in N3 stage there is a subsequent saturation around 0 of the TD.

	BKG (μV)	**TD**	**PD M**	**PD S**	**AD S**
S1	2.249	0	0.2	4	4
S2	1.781	0	0.1	4	4
S3	1.071	0.8	1	10	10
S4	15.13	0	0.05	0.7	0.7
S5	1.139	0	0.5	8	8
S6	2.099	0	0.09	2	2
S7	2.55	0	0.6	10	10
S8	1.83	0	1	20	20
S9	4.13	0	0.07	2	2
S10	1.29	10	7	30	30
S11	1.7	2	0.4	10	10
S12	1.67	0	0.3	3	3
S13	4.418	0	0.5	10	10
S14	2.5	0	0.1	2	2
S15	10.35	4	0.2	3	6
S16	1.555	0	0.6	10	10
MEAN	3.4651	1.054	0.794	8.0437	8.231
STD	3.84	2.62	1.68	7.7	7.61

Table 3.11: Turin Database. RSWA scoring with BKG1. TD: Tonic Density, PD: Phasic Density, AD: Any Density, M: Montréal Method, S: SINBAR Method.

	BKG (μV)	**TD**	**PD M**	**PD S**	**AD S**
S1	1.7360	0	0.4000	4	4
S2	1.2740	0	0.3000	7	7
S3	0.7473	3	2	20	20
S4	10.9200	0	0.0500	2	2
S5	0.8794	0	0.7000	10	10
S6	1.3860	0	0.2000	3	3
S7	1.7250	0	1	20	20
S8	1.1120	0	2	30	30
S9	3.2270	0	0.1000	3	3
S10	0.8097	20	10	40	50
S11	0.8490	4	2	40	40
S12	0.8889	0.9000	0.7000	7	7
S13	3.6280	0	0.7000	20	20
S14	1.8230	0	0.1000	3	3
S15	8.5650	4	0.2000	8	10
S16	1.1010	0	0.9000	20	20
MEAN	2.5420	1.9937	1.3344	14.8125	15.5625
STD	2.96	5.02	2.41	12.90	14.30

Table 3.12: Turin Database. RSWA scoring with BKG2. TD: Tonic Density, PD: Phasic Density, AD: Any Density, M: Montréal Method, S: SINBAR Method.

	BKG (μV)	TD	PD M	PD S	AD S
S1	0.8134	2	1	20	20
S2	0.5896	2	1	40	40
S3	0.3353	40	5	100	100
S4	4.9300	0	0.3000	9	9
S5	0.4140	60	2	100	100
S6	0.6207	0	0.7000	50	50
S7	0.7533	30	5	70	70
S8	0.5022	60	6	90	90
S9	1.4620	0.5000	0.5000	6	6
S10	0.3779	70	20	90	100
S11	0.3822	20	7	100	100
S12	0.4030	3	2	80	80
S13	1.6950	7	3	40	40
S14	0.8255	0	0.3000	20	20
S15	4.0090	20	0.7000	60	60
S16	0.4983	20	3	100	100
MEAN	1.1632	20.9063	3.5938	60.9375	61.5625
STD	1.3569	24.32	4.88	34.93	35.57

Table 3.13: Turin Database. RSWA scoring with BKG3 . TD: Tonic Density, PD: Phasic Density, AD: Any Density, M: Montréal Method, S: SINBAR Method.

3.4 EKG Removal

The effects of EKG removal on RSWA quantification are showed in this Section. The TURIN database results after applying the EKG removal algorithm are shown in Table 3.14. The EKG channel is sampled at 256 Hz (as well as the EMG) and the pre-filter is composed by a band pass filter with 0.3-70 Hz bandwidth and Notch filter centered in 50 Hz. Visual inspection of the tracings showed that subjects 3, 4, 6, 7, 8, 11, 12, 13, 14 and 16 have a clearly visible EKG artefact on the chin EMG channel. The samples marked as corrupted by EKG artifact and deleted are around 6% out of all REM samples. Comparing these scoring with the previous one (without EKG removal) it is possible to notice that it varies the most for subjects 7. The difference is significant for subjects 7, 8, 11, 13. Subject 1 presents with an unexpected variation. In general, the EKG removal procedure increases the AI value because it deletes high amplitude samples. These differences are highlighted in Figure 3.8. The same comparison is done on the Tonic Density. Normal TD and TD computed after the EKG removal is shown in Figure 3.9.

	R REM (%)	**AI**	**BKG (μV)**	**TD**	**PD M**	**PD S**	**AD S**
S1	5.1	0.8088	1.3450	0	0.5000	6	6
S2	5.9	0.9535	0.9801	0	0.4000	10	10
S3	5.4	0.9439	0.5690	3	3	20	30
S4	5.8	0.1670	8.3000	0	0.1000	3	3
S5	6.9	0.9466	0.6817	0	0.9000	30	30
S6	5.4	0.9761	1.0490	0	0.3000	4	4
S7	6.5	0.4470	1.2880	0.6000	2	30	30
S8	6.4	0.7074	0.8481	2	3	40	40
S9	5.3	0.9590	2.4600	0	0.2000	3	3
S10	6.0	0.6614	0.6257	20	10	50	60
S11	4.1	0.9238	0.6452	5	3	20	20
S12	6.4	0.9749	0.6767	0.9000	1	10	10
S13	5.2	0.0879	2.8000	2	1	20	20
S14	5.9	0.9859	1.3870	0	0.1000	3	3
S15	4.9	0	6.6270	4	0.3000	20	20
S16	7.4	0.8623	0.8417	0	1	30	30
MEAN	5.8379	0.7128	1.9453	2.3438	1.6750	18.6875	19.9375
STD	0.8334	0.3450	2.2670	4.9751	2.4572	14.3560	16.1636
P(AI>0.9)		50 %					
P(AI<0.8)		37.5%					

Table 3.14: Turin Database. RSWA scoring with EKG Removal. R REM: Percentage of REM samples removed, TD: Tonic Density, PD: Phasic Density, AD: Any Density, M: Montréal Method, S: SINBAR Method.

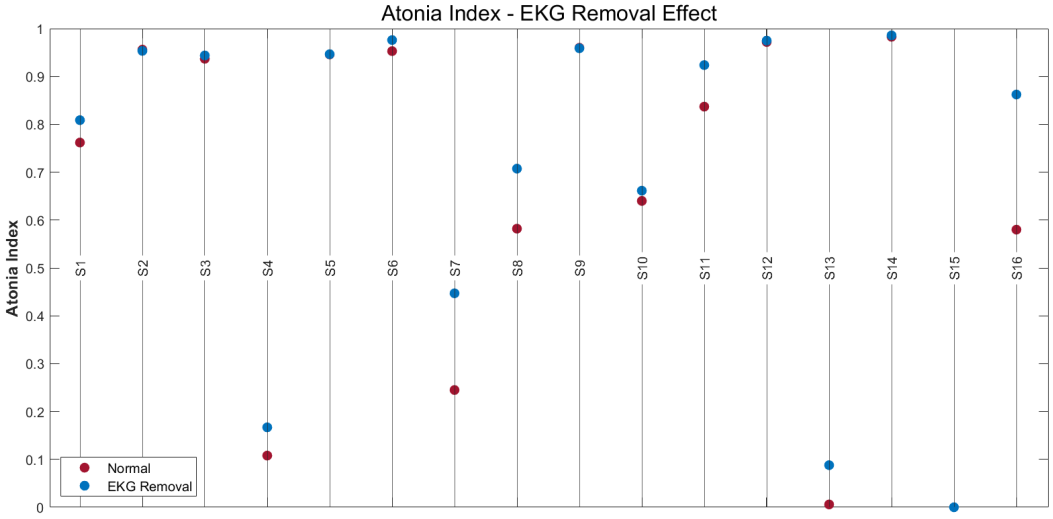

Figure 3.8: TURIN Database. RAI scoring. Normal vs EKG Removal.

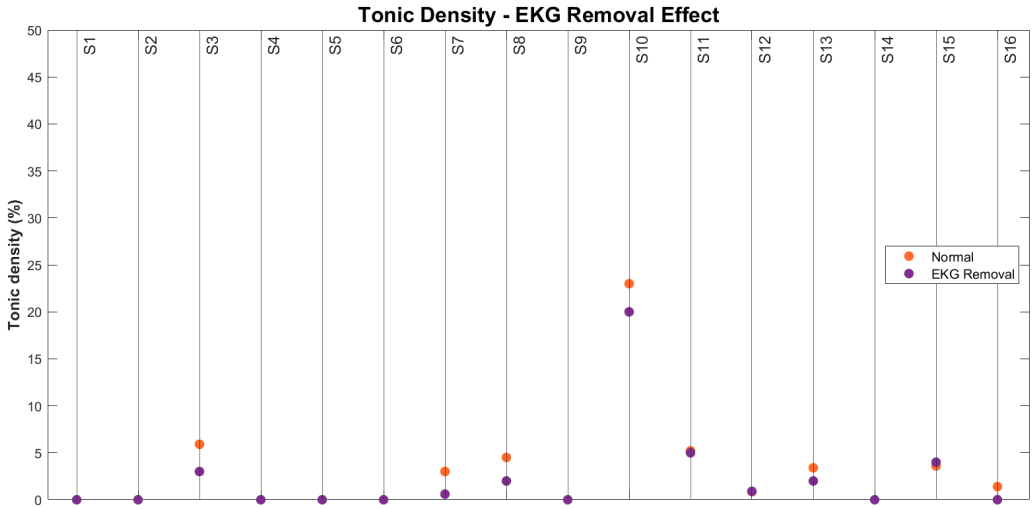

Figure 3.9: TURIN Database. Tonic density scoring. Normal vs EKG Removal.

Chapter 4

Discussion and Conclusion

This thesis work presented an algorithm to calculate the muscle parameters used to quantify muscle atonia during REM stage in an automatic manner. The algorithm follows as closely as possible the methods found in literature and the international guidelines. Evaluations of REM Sleep Without Atonia in literature are mainly based on the visual quantification methods, Montréal and SINBAR, currently in use in clinic. Several automatic methods are gaining ground and in this work the REM Atonia Index presented by Ferri was also implemented. Impairment of muscle atonia during REM sleep, in addition to being a disorder in itself, is also linked to the diagnosis of REM Behaviour Disorder, and has generally been correlated with neurodegeneration. At this time, RSWA and RBD, when isolated, are considered prodromal symptoms of neurodegenerative diseases, but the evolution is yet to be explored. The need for parameters capable of objectively describing this loss of atonia during REM is therefore crucial. The aim is also to establish a measure that can describe the progression of neurodegeneration.

Three databases were used for this work: two provided by the Sleep Disorders Centre of the A.O.U. Molinette of Turin, Italy, while the other is excerpted from the CAP Sleep Database, made available in open access on PhysioNet by the Sleep Disorders Centre of the Maggiore Hospital of Parma, Italy. The REM Atonia Index has been implemented following the indications found in literature. It is a method based on a fixed amplitude value, which accounts for the amount of samples that have an amplitude less than 1 μV (considered as muscle atonia) in 1s-epochs. Overall, the RBD patients showed very low RAI and in more than 92% of the cases below the indicative pathological threshold of 0.8 in the CAP database. However, it is not known whether the high amplitude depends on the condition of the subject or on the sampling and recording conditions (also it is important to notice that the database comes from a 20-year-old study). In the Turin database, approximately 43% of subjects achieved an AI greater than 0.9, indicative of preserved atonia. As we do not know the pathological condition of the subjects, it is not possible to

know if this result is consistent; however, unless the signal recording is completely mis-set, or absent (e.g., electrode disconnected), night events, motion artefacts or noise are unlikely to significantly decrease the overall signal amplitude. Regarding the Vortioxetina database, four subjects out of nine (s1, s3, s4, s8) showed very similar AI value in the two recording. Considering that they are healthy subjects and that the drug effect on atonia is still under evaluation and in any case limited, these results seem the most reliable. In the end, the evaluation of the effect of Vortioxetine on REM atonia for the subjects was inconclusive.

The implemented automation of the visual methods allowed the calculation of phasic and tonic densities according to the indications of the Montréal and SINBAR methods. Densities represent the percentage of REM epochs that meet the definition of tonic/phasic out of all REM epochs considered (i.e., events excluded). These definitions are based on the estimation of the subject's background muscular activity, as an amplitude value, and relay on overcoming an amplitude threshold established by it. This makes the method free of a-priori defined absolute amplitude thresholds and adapts the value to each subject. However, this value is established by the sleep technicians on the basis of the specific trace and of their expertise (e.g. the operator visually recognises which part of the trace is a muscular activation and then assesses its amplitude) and there are no absolute rules specifying how to establish it precisely. Therefore the background activity assumes a value dependent on the operator rather than on an actual objective measure. This can still produce consistent results between different operators, but makes it difficult to translate the method into an algorithm. Moreover, the results obtained show that the typical muscle tone of the subject is not the only parameter to be taken into account in the evaluation of the epochs. Indeed, the algorithm produces very high density values even when the trace presents amplitude characteristics that are not related to the characteristics of the subject but rather to the recording or the recording conditions. For example, if the subject moves in bed at night and presses an electrode, this will produce a change in the amplitude of the recorded signal, but does not represent a different muscle tonic activity. The same applies to the respiratory artefact, which sometimes creates a clearly visible envelope on the trace. A fixed amplitude threshold is therefore mathematically meaningless unless accompanied by medical knowledge. Hence, it is evident that the description of nocturnal events to be excluded from the analysis, such as arousals or rhythmic movements, should be extended to all those moments in which the trace is not regular, but this introduces (as well as being very time consuming) subjectivity in the identification of these events. Anyway, the evaluation of the algorithm on varying estimates of the BKG activity has shown that the value closest to the visual estimate of the resting muscle tone is around the median of the rectified signal. However, employing this type of threshold (or higher) leads to a saturation towards zero in the density's values.

Finally, by observing the traces in the various databases, the problem of the

EKG artefact emerged; indeed, many subjects feature, in correspondence of the greatest muscular relaxation, the cardiac complex with significant amplitude. This waveform is difficult to remove with filtering because it is partially superimposed in band with the EMG signal. In addition, the use of very restrictive filters changes the amplitude in the passband due to the ripple, thus making the signal unusable for this type of amplitude-based method. The Turin database has several tracks with this artefact and the results calculated following the EKG artefact removal procedure implemented here showed very different AI values for subjects 7, 8, 11, 16 (AI increased by about 0.1 to 0.25) which indeed showed strong EKG corruption. Tonic density, on the other hand, is modified mainly for subjects 3, 7, 8 and 10 (increase of about 4 percentage points). The graphical display of the detection of the EKG artefact in the EMG trace seems satisfactory, taking into account the limitations already mentioned.

The importance of these metrics in describing atonia is clear, as much as their automation, but the latter presents considerable challenges, especially in the case of faithful automation of visual methods used in the clinic, given their link to amplitude assessments. This thesis work implemented the literature metrics in an automatic scoring algorithm, providing an open-access method for scoring REM anomalies. Future works should address a robust clinical validation of such automated measures, as well as the implementation of a global, objective score which accurately describes lack of atonia during REM Sleep.

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