Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Information Technology and Electrical Engineering
Department of Engineering Cybernetics

Ole Drange

Source localization of pre-REM negativity

Master's thesis in Cybernetics and Robotics
Supervisor: Marta Molinas
Co-supervisor: Andres Felipe Soler Guevara
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Abstract

Rapid eye movements (REM) during sleep is a descriptor of the REM sleep stage, it is well known that REM sleep plays an essential role in sleep. Therefore, precisely locate the source activity before the REM can help elucidate the brain areas involved to produce this important event. This study aims to find the source activation in the pre-REM negativity. To do so, the onsets of the eye movement were required. An algorithm to detect the eye movement onsets was firstly developed and evaluated in sleep and awake data, then, the source reconstruction of the pre-REM activity was found. Afterward, a T-test was implemented to find significant activation during pre-REM negativity. The dataset used in the study was registered by the Human Sleep Lab of the International Institute of Integrative Sleep Medicine and was analyzed using the MNE open-source python package. The algorithm is an improved method based on a previously made eye movement algorithm by Takahashi in 1997. The results showed that the algorithm had a recall of 0.97, a precision of 0.69, and an F1 score of 0.80. Additionally, the new algorithm was tested for categorizing the REM sleep stage, where this approach was found to identify REM sleep in whole night recordings. To localize the pre-REM negativity, two methods of source reconstruction were implemented and the areas with significant activation in the pre-REM negativity were identified. The results suggest that the pre-REM negativity has the most significant activation in the striatum and the orbitofrontal regions.

These results show that the algorithm can find eye movements in REM sleep and find the REM sleeping stage. However, improvement of the algorithm is needed before the algorithm's output can be trusted without a visual inspection of the results. Source activation in the striatum and orbitofrontal regions indicates the brain's use of a reward or punishment, and a decision-making process of the brain is active. For further research, looking at the algorithm criteria and increasing the algorithm's precision is recommended. The Pre-REM negativity's effect in REM sleep should also be researched further to find more connections to brain disorders.

Sammendrag

Raske øyebevegelser (REM) under søvn er en beskrivelse av REM-søvnstadiet, det er velkjent at REM-søvn spiller en viktig rolle i søvn. Derfor å finne nøyaktig hjerne aktivering før REM kan bidra til å belyse hjerneområdene som er involvert for å produsere denne viktige hendelsen. Denne studien tar sikte på å finne hjerne aktivering i før REM aktiviteten. For å gjøre det er det nødvendig å finne start tiden for øyebevegelsene. En algoritme for å oppdage øyets bevegelsesutbrudd ble først utviklet og evaluert i søvn- og våkne data, deretter ble hjerne aktivering av før REM aktiviteten funnet. Etterpå ble en T-test implementert for å finne betydelig aktivering under før REM aktiviteten. Datasettet som ble brukt i studien ble registrert av Human Sleep Lab fra International Institute of Integrative Sleep Medicine og ble analysert ved hjelp av MNE åpen kildekode-python-pakke. Algoritmen er en forbedret metode basert på en tidligere laget øyebevegelsesalgoritme av Takahashi i 1997. Resultatene viste at algoritmen hadde en tilbakekalling på 0,97, en presisjon på 0,69 og en F1-score på 0,80. I tillegg ble den nye algoritmen testet for å kategorisere REM-søvnstadiet, hvor denne tilnærmingen ble funnet å identifisere REM-søvn i hele nattesøvnen. For å lokalisere før REM aktiviteten ble to metoder for hjerne aktivering implementert, og områdene med betydelig aktivering i før REM aktiviteten ble identifisert. Resultatene antyder at før REM aktiviteten har den viktigste aktiviseringen i striatum og de orbitofrontale regionene.

Disse resultatene viser at algoritmen kan finne øyebevegelser i REM søvn og finne REM søvn stadiet. Imidlertid er forbedring av algoritmen nødvendig før algoritmens resultat kan stole på uten visuell inspeksjon av resultatene. Hjerne aktivering i striatum og orbitofrontal regioner indikerer hjernens bruk av belønning eller straff, og en beslutningsprosess i hjernen er aktiv. For videre forskning anbefales det å se på algoritmekriteriene og øke algoritmens presisjon. Før REM aktiveringen i REM søvn bør også undersøkes nærmere for å finne flere forbindelser til hjernesykdommer.

Preface

The knowledge background used for this paper is mainly from TTK4551, TTK4555, TDT4120, and TDT4240. TTK4551 is the specialization project that is the foundation of this project, and section introduction and theory is reproduced and elaborated from TTK4551. TTK4555 gave me the signal processing knowledge i needed, and TDT4120 and TDT4240 gave me the main programming knowledge used. The programming language used is python and the main packages used is the MNE for exploring, visualizing, and analyzing human neurophysiological data, Numpy and Pandas for scientific computing and data analysis, and Matplotlib for visualization. The data set used was provided from Human Sleep Lab of the International Institute of Integrative Sleep Medicine in Japan, and contained eight subjects.

I would like to thank my supervisor Professor Marta Molinas for guidance and overall support for this project. I would also like to thank PhD candidate Andres Felipe Soler Guevara for the great support, guidance and interest he has shown in this project. Furthermore, would i like to thank Junya Furuki and Takashi Abe for excellent collaboration with sleep data, eye movement knowledge and providing the corrected eye movements for the data sets.

Table of Contents

List of Figures

List of Tables

Acronyms

EEG Electroencephalogram.

EM Eye movement.

EMG Electromyography.

EOG Electrooculography.

HdEEG High density EEG.

LdEEG Low density EEG.

MRI Magnetic Resonance Imaging.

PSD Power spectral density.

REM Rapid eye movement.

sLORETA standardized low resolution brain electromagnetic tomography.

1 Introduction

1.1 Background and motivation

Electroencephalogram (EEG) is a method to record brain signals. The signals are picked up by electrodes (sensors) placed on the head's scalp that record electrical voltages. These signals are then used to reconstruct brain activity. And by analyzing brain activity, it is possible to identify if a patient has a brain disease. The most common brain disease to detect and investigate with EEG is epilepsy [6]. Other uses for EEG are identifying memory problems such as dementia, head injuries, and brain tumors. EEG is a cheap method to acquire and a good indication of brain activity [7]. It has a high temporal resolution, reaching a sub-millisecond time scale witch is why it's the standard technique in sleep research. Over the last years have computer programs and techniques to reconstruct brain activity improved a lot but research on Eye movement (EM)s in Rapid eye movement (REM) sleep has fallen behind. This is why an algorithm to find EMs in REM sleep, making it easier and less time-consuming to do research on is in focus in this paper.

EEG was first used on humans in 1924,[8] while the first description of eye movements associated with EEG and dreaming was made in 1953 by Aserinsky and Kleitman 29 years later. Eye movements are a characteristic that defines the REM sleep stage [9], and parameters associated to REM sleep, such as REM density [10], and pre-REM negativity [11, 12] has been associated with the functional role of REM sleep. REM sleep helps with memory [13], and emotional processing [14]. Other studies have also suggested a link between depression, post-traumatic stress disorder, and chronic sleep deprivation with alterations in the REM sleep pattern [15, 16, 17, 18]. In this report, the focus is on brain activation in REM sleep before and after the onset of EMs, which have been linked to specific neural activation in the brain [12, 19, 11]. These works clearly point out the relevance of identifying the exact timing of the rapid eye movement onset and how the neural paths around the time immediately before and after onset can illuminate the potential functional role of REM sleep.

1.2 Previous work

Precise timings of EM onsets is really important in REM stage EM studies. The most common method to find EM onsets is to manually inspect the raw data, and that is a tedious process that makes EM research unpopular. Takahashi has made an algorithm to find EM onsets shown in [3], and this study is the starting point of this paper. Other studies on EMs in REM sleep are [19, 20]. Both of these studies are done in Low density EEG (LdEEG). In this paper a similar approach to finding the significant activation of pre-REM negativity is tried out with High density EEG (HdEEG). Studies using high-density EEG in sleep research has been done before. The study [21] found that high-density EEG can be used to study brain functioning in neurological and neurodevelopmental disorders and to evaluate therapeutic approaches, while [19] found activity in emotion, memory, and motor-related brain locations in REM sleep.

1.3 Scope of this paper

This report was focused on making and implementing an algorithm to find EMs in the REM sleeping stage. Then use the EMs for source localization, and find statistically significant brain activation points in pre-REM potentials compared to baseline. The algorithm was tested on eight subjects and given a score in precision, recall, and F1. The algorithm was also tested on a subject in the awake state for finding EM onsets in a visual task done by the subject, and REM stage finding for a full night of sleep was also be tested by the algorithm. Two different methods for finding statistically significant brain activation is shown, and the differences in the method and results were shown.

1.4 Organization of this paper

This report starts by presenting the materials and method behind sleep, eye movements and source reconstruction. Afterwards, EM detection is presented. This is a section about how the EM detection algorithm is made, the results and discussion of the algorithm. Then Scoring of REM sleeping stage is presented. This section presents how the algorithm can be used to find the REM sleeping stage, and what results it got. Lastly in this section is the results of REM sleep stage is discussed. Then source localization of the pre-REM activation is presented. This section contains all the steps needed to find the source localization, the results of two methods for finding the significant source localization of pre-REM activation, and then discussion about the results found are presented. Lastly, conclusions and future work is presented.

2 Materials and Methods

This section contains the theoretical background needed to produce the results in this paper. This section was reproduced and elaborated from the specialization project [22].

2.1 Electroencephalogram

An is a method of recording brain activity. It uses electrodes on the scalp of the head to record electrical voltages. The voltages comes from the neurons in the brain that uses electrodes to communicate with each other. The moving electrodes changes the voltages in the brain that can be picked up with electrodes on the scalp of the head. The voltage for a resting neurons is in the range of 70 millivolts, and when they pass through different brain tissues and layers between the brain and the scalp, they are reduced even more. It is so small voltages that it is hard to differ from noise. It is needed to filter out the noise before the brain activity can be localized. Localization together with the intensity and time-course of the sources is called source reconstruction.

2.2 Sleep

Sleep has four stages. N1, N2, N3, and R. Stages N1 and N2 are often combined under light sleep. Stage N3, commonly known as deep sleep, and R is commonly known as REM sleep, or rapid eye movement sleep [23]. When we sleep, we go through a cycle of all these stages. Normally we start in stage N1, which is the lightest sleep, and easy to wake up from. Then we move to stage N2 after 10-20 minutes, which is a middle stage we need to be in before our body goes to N3 or deep sleep. Deep sleep is where our body is "repairing" the body the most. It is recommended to get about 20% of our sleep in a deep sleep. When our body goes to deep sleep, our brain frequency is the lowest of the four stages, and the amplitude of the brain signals is the highest. The length of N3 is reduced for each cycle we have gone through. From N3, we move back to N2 and then into R. This is a full cycle of sleep and normally takes 1.5 hours. It is in REM sleep we dream, and the R stage gets longer and longer the more cycles we have been through. From R, we go back to N2, and then we move between N2 to N3 to N2 to R. So N2 is a middle stage we need to go into to go from R to N3 or N3 to R. These stages is not distinct entities, and we do not jump for one to another one. We gradually move between them and are they are just a way of differentiating the sleep process.

2.3 Sleep waves and scoring

There are four main waves in sleep, Alpha, Beta, Delta, and Theta. The frequency of the waves classifies them. Beta waves have the fastest frequency between 14 and 30 Hz and are present during wakefulness and drowsiness. It also reemerges during REM sleep. Alpha waves have frequencies between 8 and 13 Hz and are seen during quiet alertness with eyes closed. Theta wave frequencies are between 4 and 8 Hz and are the most common sleep frequency in EEG waves. Delta waves have frequencies between 0.5 and 2 Hz and are most common in deep sleep. In addition to these waves, sleep spindles and k complexes are used to score the sleep. Sleep spindles originate in the central vertex region and are in the frequency range of 11-16Hz. K complexes are slow and sharp waves that start with a spike in the negative direction before spiking positive. Both sleep spindles and k complexes are an indication of N2 sleep but can be seen in other stages too [1]. Vertex sharp waves are also used to classify sleep. These waves are sharply negative-going bursts that stand out from the background. And lastly, slow waves are high amplitude and low-frequency variants of delta waves. These are the defining characteristics of N3 sleep. An example of the sleep waves can be seen in Figure 1.

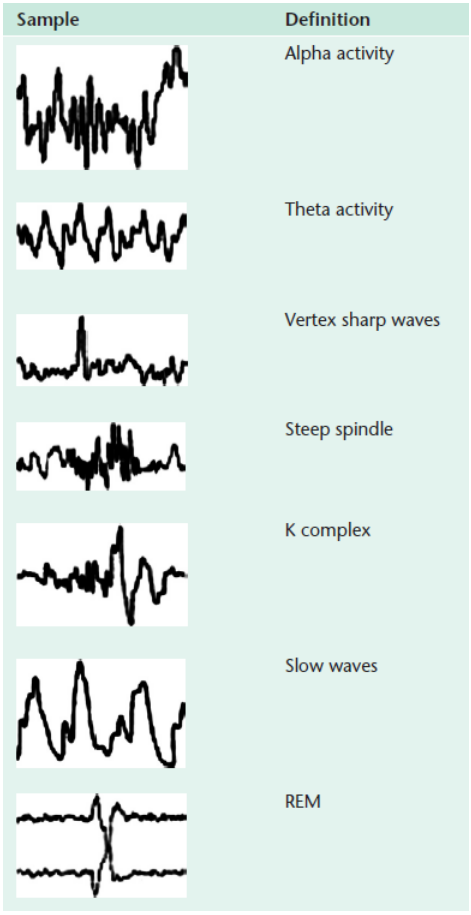


Figure 1: Example of how brain waves look in EEG sensors [1]

Sleep, as mentioned in the sleep subsection, is a cyclic state. This means we can use this knowledge in the scoring. Firstly, the first several minutes of EEG recording will be in an awake state. After the awake state, we know that the subject moves on to state N1. As seen from table 1 N1 are normally 1-5 min long. From N1, the subject can move back to awake, but normally the next stage is N2. The subject will now move between N2 and N3 before going moving from N2 and REM. This cycle can be seen in Figure 2

To classify sleep with a visual inspection, the brain activity and the time of the sleep cycle are used. The start of the sleep recordings in the awake state. The awake state consists mostly of alpha activity, but when the subject moves, beta activity is also seen. Movement can also cause artifacts shown as spikes in all channels as EEG sensors are susceptible. Stage N1 is characterized by low voltage and fast EEG activity. Theta activity is the dominant wave in this stage but is seen together with low amplitude beta waves. At the end of the N1 sleep stage, Vertex sharp waves may occur, but if sleep spindles or k complexes are observed, the sleep will not be classified N1. Stage N2 is also dominated by theta waves and can have occasional bursts of faster activity. In this stage, K complexes and sleep spindles are typical and normally occur in an episodic fashion. In stage N3 sleep, slow waves with high amplitude are seen. It is also normal for eye movements to cease altogether. In Stage REM, the amplitude of the signals is reduced. It contains a mix of frequencies with theta, alpha, and delta waves. But the Rapid eye movements are the simplest to spot and are seen in the EOG. Physiological activity is also significantly higher, and pulse and blood pressure may increase. The complete protocol and procedure for scoring sleep can be found in [24] where the information of equipment, protocol and scoring is given.

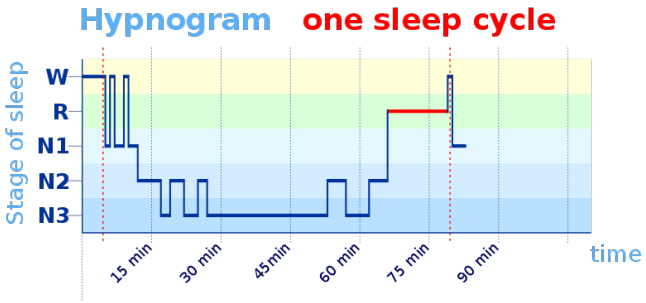


Figure 2: Normal sleep cycle [2]

Sleep Stages	Normal Length
N1	1-5 minutes
N2	10-60 minutes
N3	20-40 minutes
REM	10-60 minutes

Table 1: Table for normal sleep length in sleep stages [5]

2.4 Eye movement in REM sleep

There are four basic types of eye movements. The different types are saccades, smooth pursuit movements, vergence movements, and vestibulo-ocular movements [25]. The eye movement in the REM sleeping stage is saccades. Saccades is a rapid eye movement that abruptly changes the point of fixation. Finding EM in REM sleep is a long and time consuming task. This leads to few peoples wanting to do research on task that needs precise EM location. Many research fields in EEG and sleep have gone along way the last years but few of them have focused on EMs. This is believed to be because of the long and boring task of finding the EMs. So to increase the research speed on EMs and REM sleep an automatic EM detection algorithm is believed to help. An EM is seen in figure 3. In the figure, the EM is marked with a dotted line and the channels EOG-left and EOG-right are plotted in black. The figure shows that the two channels move or spikes in opposite direction. To be categorized as an EM both channels needs to spike in opposite directions with a slope of 250 μV per second. This spike has to last for less then 0.5 seconds and need to have an amplitude of more then 30 μV.

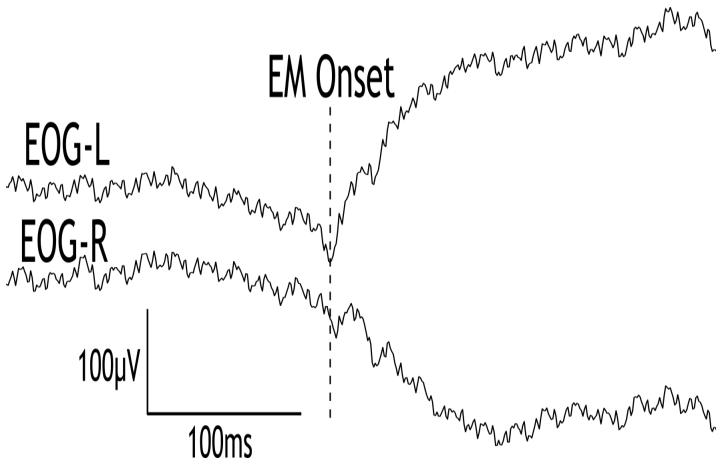


Figure 3: Image shows how EMs look on channel EOG-Left and EOG-Right

When researchers need to find EM with out the algorithm. They need to look at small time ranges

and mark them precisely. This process takes about 1 day to mark the EMs of a single persons one night of sleep.

2.5 Data set

This project uses a data set with HdEEG from the Human Sleep Lab of the International Institute of Integrative Sleep Medicine (`https://wpi-iiis.tsukuba.ac.jp/japanese/news/1340/`). The data set is obtained with Polynomnography recordings in 8 subjects and is recorded with a sampling rate of 1024Hz. The data set contains a total of 136 channels, 128 channels, 2 mastoid channels, 3 Electromyography (EMG) channels, and 3 Electrooculography (EOG) channels. The EOG channels are electrodes placed under, left, and right of the eyes. The electrode left and right of the eyes are used in the algorithm to find eye movements. EMG channels are channels that pick up muscle movements that can be used to reduce muscular noise in the signal. The position of EOG-left, EOG-right, and EMG-chin electrodes are shown in figure 4.

The data set also contains one of the subject's awake period. In this period the subject was tasked with eye movements, and the same sensor setup as the sleep recordings was used. This was used to test the algorithm for finding EM during awake state.

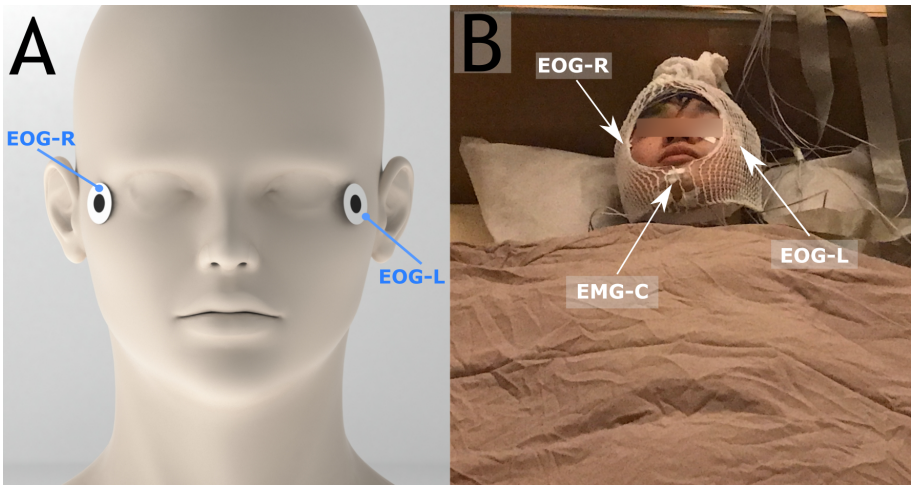


Figure 4: Shows where the EOG-Left, EOG-Right, and the EMG-chin is pleased while recording the sleep data

2.6 Power spectral density

Power spectral density (PSD) is the energy of a signal at different frequencies. In other words, how much power all specifics frequencies in a signal have. This can be found by using the Fast Fourier transform (FFT). FFT is a method that converts a signal from the time-domain to the frequency domain. FFT is calculated using a version of the Discrete Fourier transform. This can be mathematically formulated as $X_k = \sum_{n=0}^{N-1} x_n e^{-i2\pi kn/N}$, $k = 0, ..., N-1$. Discrete Fourier transform requires $O(N^2)$ operations, and this is why FFT is used. This method takes advantage of repeated calculations in discrete Fourier transform and cuts the operations down to $O(Nlog(N))$.

PSD can be used to analyze the signal and find out what frequencies has the most energy. This is useful in sleep research as the waves' frequency categories the sleep and can be used to find abnormal activity in the brain.

2.7 EEG Forward problem

In EEG, a forward model is a way of modeling how signals from the brain are detected in the sensors outside the head. The model considers sources in the brain and establishes the portion of the source signal that is registered by the electrodes. This model can be used to simulate what electrodes will detect with different brain activity. To make this forward model, information about the subject's head is needed.

Two main components are needed to make a forward model, the head model from the Magnetic Resonance Imaging (MRI) and the sensor positions. Firstly the head model is described. A head model holds information about how an electric current spreads throughout the head. To find the electric current movements, the electric resistance in the head needs to be found. The electric resistance is different in different elements in the head, so firstly, the head elements' composition is needed. Because humans have different shapes and forms of heads, the head elements' composition is different in every individual. This means that everyone has a unique head model. Usually, to find this model, MRI is used. MRI is an instrument that scans your head and outputs images of how the head is composed. If it's not possible to get an MRI of the patient's head, you can use a template MRI. Template MRI is a standard MRI that is made by averaging multiple heads, making a model that best fits an average head. In this study, the 'fsaverage' Template MRI was used. "Fsaverage" is a model provided by FreeSurferWiki [26], that is made by a combination of 40 MRI scans of real brains.

After the head model is found or a template is used, information about the sensors and the source signal is needed. For the sensors, the position on the surface of the head is needed. And for the source signal, position and amplitude are needed. The sensors are typically placed in the five percent system or the 10-20 system [27]. These systems were made to make it easier to reproduce and analyze EEG data. The electrode position system is typically saved with the data set. In this study, the forward model was used to calculate the inverse model. The forward model can be used as a tool to test out different brain activities. Using the forward model to simulate brain activity can be compared to a wanted source reconstruction to check if correct.

The forward model is stated as $M = GD + n$. Where M is the matrix of data measurements at different times, D is the matrix of dipole magnitudes at different time instants. G is the lead field that describes the current flow of the electrode through each dipole position know as the gain matrix, and n is the noise. [28]

2.8 EEG inverse problem: Source reconstruction

Source reconstruction is a method using electrode input to estimate brain activity. This is done by using the inverse model. The inverse model is, as the name says, the inverse of the forward model. The input to the inverse model is electrode signals, and the output is brain activity.

The inverse model is stated as $\hat{D} = MG^{-1} + n$. Here is $\hat{D}$ the estimation of the dipole magnitude matrix, M the electrode matrix, G^{-1} the inverse of the gain matrix, and n the noise. This has equation has infinite solutions.

When we have found the inverse model, we use it to calculate the source. The problem with the inverse solution is that the problem doesn't have a unique solution. This means we need to make assumptions to get the best solution. [29] These assumptions can be incorporating different constraints based on a priori information about the desired source or physiological assumptions. It exists many different methods of making source reconstruction. Some examples of these methods are found here [30], but in this project, we will use the standardized low resolution brain electromagnetic tomography (sLORETA) method. This method solves the infinite solution problem by focusing on the localization error and not the source strenght. sLORETA gives zero localization error and is therefore often used [31]. More details about this method can be found in the paper [31]

2.9 Statistics

To find statistically significant results a statistical test is needed. Comparing two sets of values often uses the T-test, also known as the student's t-test. T-test is a statistical test that checks if a pre defined null hypothesis holds, and is the most used statistical test for checking if two sets of data are significantly different from each other [32]. When the two data sets comes from the same selection or if the sets have high correlations between them a paired t-test is used. The procedure for doing a paired t-test is [33]:

Step 1: Calculate $d_i = y_i - x_i$, d_i is the difference between the two observations in each pair, y_i is the value in the first set and x_i is the value in the second set.

Step 2: Calculate the mean difference $\bar{d}$

Step 3: Calculate the standard deviation of the differences $SE(\bar{d} = \frac{S_d}{\sqrt{n}}$

Step 4: Calculate the t-statistic $T = \frac{\bar{d}}{SE(d)}$

Step 5: Use tables of the t-distribution to compare your value for T to the t_{n-1}

The p-value found by taking the t-test shows how likely the two sets have the same value distribution. If the p-value is less than 0.05, giving less than 5% chance of the sets having the same value distribution, the two sets are seen as a significant differences from each other.

2.10 Software

The programming language used is Python and the main packages used is the MNE package [34] for exploring, visualizing, and analyzing human neurophysiological data, Numpy [35] and Pandas [36] for scientific computing and data analysis, Matplotlib [37] for visualization, and SciPy [38] for scientific calculations.

3 EM Detection

In this section will the method, results, and discussion of EM detection be presented. The section starts by explaining the method/ algorithm used to get the onsets of eye movements in sleep stage REM. Then improvements made to the algorithm are presented before showing the results. Lastly, the results and method are discussed.

3.1 Eye movement detection base algorithm

EM detection is normally done manually, which is a long and tedious process. Because of this problem with manual EM detection, an algorithm was made to avoid this problem. A method describing how an algorithm can do it is found in the paper [3]. As this is an old paper (more than 20 years ago), making an improved algorithm based on the method described in the paper is started. The detection of eye movement in the paper starts with the definition of 3 basic REM-related EOG parameters: amplitude, duration, and slope of the EOG trace. Following the procedure [3], the raw REM data is re-sampled at 80hz, and a 7 point linear weighted moving average is applied to the data. Then the double derivative is calculated using NumPy in python from [35]. Afterward, using the double derivative, spikes such as seen in the figure 5, are identified by the algorithm (points A and B). Point A is the starting point of the slope and is found by the double derivative's first spike. Point B is the ending point of the slope and is the first spike after point A in point A's opposite direction. With all points A and B identified, the following three criteria are observed for the definition of EM onset:

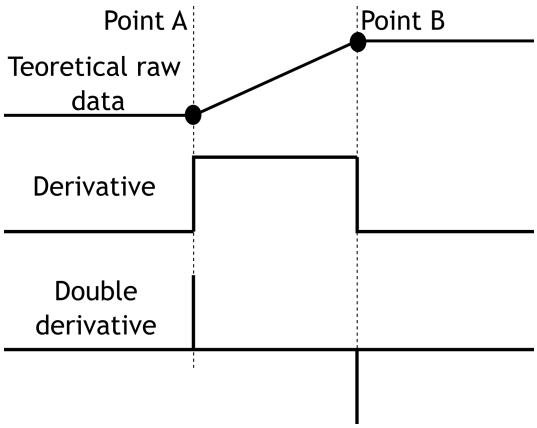


Figure 5: Shows how point A and B are correlated to the double derivative of the signal

- All point pairs (A and B) with an absolute value of point B minus point A higher than 30 microvolts are accepted.
- The slope between the point pairs has to be higher than 248.3 microvolts per second.
- The slope duration has to be lower than half of a second.

Points that fulfill all these three criteria are then saved as EM and used accordingly. The problem with this method was that the data contain much noise. Taking the double derivative of a signal with noise leads to many unwanted spikes in the double derivative. These spikes are mistakenly accepted as EM points by the algorithm and lead to many unwanted confirmed EM onsets. A Low-pass filter was used instead of a linear weighted moving average to avoid the noise spikes, but this lead to unprecise marking of the EMs. Low-pass and moving average was also implemented together, but the results obtained with this approach were still ineffective in capturing the EM onsets correctly. This problem with precision is due to the smoothing of the signal. After the signal is filtered with a low-pass filter, some of the spikes in the double derivative were misplaced

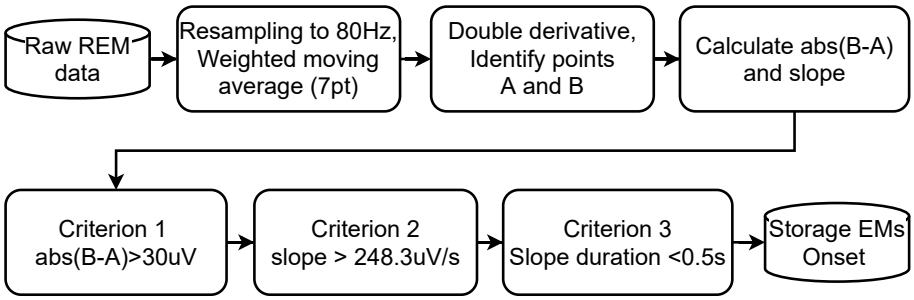


Figure 6: Overview of Base Algorithm procedures according to [3]

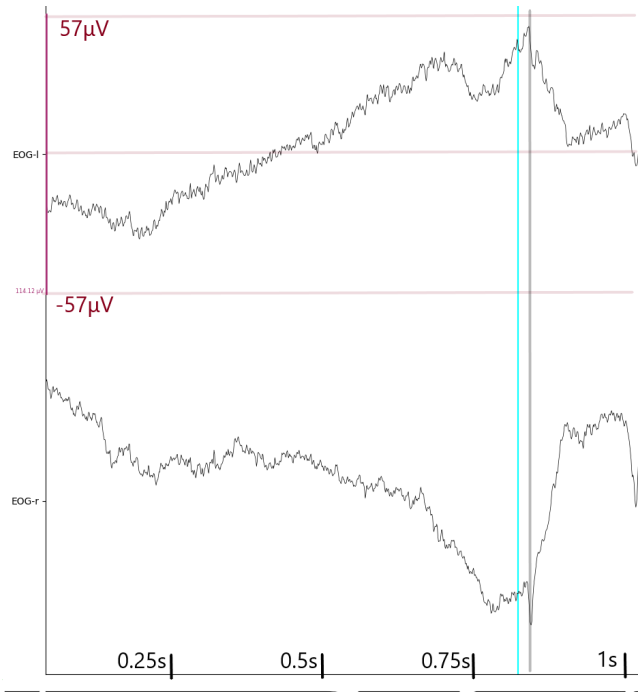


Figure 7: Example of unprecise point marked by the base algorithm. The blue line is the point marked by the algorithm and the black line is the where the EM onset is

compared to the raw signal. This misplacement leads to point A being marked close but not exactly on the actual EM starting point. As the EMs needs to be marked at the precise starting point of the onset, these results were not precise enough. An example of this imprecise placement can be seen in figure 7. The figure shows the algorithm pleased the onset on the light blue line while the actual onset is on the black vertical line about 30ms later. The lack of accuracy with this method has led to a new version of the algorithm to detect the EMs onset more accurately.

3.2 Eye movement detection improved algorithm

To improve the base algorithm efficacy in accurately identifying the EM onsets, more information from the shape and morphology of eye movements is incorporated into the algorithm. In this version of the algorithm, the use of the double derivative to find the start and stop points of the EMs is avoided. Instead, the algorithm starts with subtracting channel EOG-R from EOG-L and then resampling the data to 300 Hz. Afterwards, it uses a linear weighted moving average with a 26 step length to smoothen the data. The linear weighted moving average limits the noise and gives better results than a low pass filter. After smoothing the signal, the derivative and double derivative are calculated.

Instead of using the double derivative spikes to find points A and B, this new method checks all points in the channel arrays. This means that all 300 points per second are checked for 3 criteria.

The first criterion for the approved EM point is that the amplitude change must be greater than 80 microvolts in less than 400 milliseconds. The second criterion is that the slope has to be higher than 500 microvolts in the slope's starting point. The third criterion is that the average slope after the starting point has to be over 500 microvolts for the following 37 points. Then points that are approved by all three criteria are added to a list. These criteria are re-derived for this case from the individual EOG parameters and threshold values that constitute a well-defined REM-related EOG deflection according to [3]. As this algorithm checks every point, a series of points per EM is often accepted. This comes from the high amount of sample points that makes the points very close in time to each other and therefore has little change between them. As it is bad to get more than one accepted point per EM, the algorithm checks the gap between the approved EM points. All EM points approved except the first must have a 200 milliseconds gap from the last EM where the criteria are not met. The reason for the gap to have unmet criteria is to avoid multiple EM points in a long EM while also capturing all the small close EMs.

After the algorithm has only one point per actual EM, the position of the points is optimized. To optimize the points, the double derivative is used. The algorithm now moves the points to a local maximum of the double derivative. The maximum movement of an EM point is 62 milliseconds forward or backward in time. Lastly, the algorithm checks for sudden deflections in the recordings of EOG-L and EOG-R channels in opposite directions. EMs that do not have two individual jumps in opposite directions in the EOG-L and EOG-R channels are removed. EMs needs to have an individual spike of 40 microvolts to be accepted.

Because of the high noise and the lack of a low pass filter, the algorithm is set up so that every step where the algorithm checks for a value over a criterion, a mean of 5 points is used instead of just that specific point. This eliminates some of the noise spikes that randomly get accepted by all the criteria.

3.3 New, improved individual eye movement criteria

A visual inspection of EMs marked by the algorithm leads to further development of the algorithm. Specifically, the method looking at individual EOG-left and EOG-right channel spikes. The visual inspection showed that some of the EMs it marked were not EMs and should not be marked. With this problem in mind different test was done on the opposite spike function to see if it could be improved. Before this improvement, the algorithm looked at EMs and checked if both the EOG-left and EOG-right channels had an amplitude change in the opposite directions from each other, in the time span from EM onset to 300ms forwards. First, an approach of dividing the 300ms times span into smaller 50ms time spans and check how many of these time spans the channels move in opposite directions. An image of this can be seen in figure 8. This image shows how the method did not capture this EM because of the big negative spike at the onset of the EM. The image also shows that the last 3 segments do not necessarily have any spike movement in them and are therefore not useful for finding EMs.

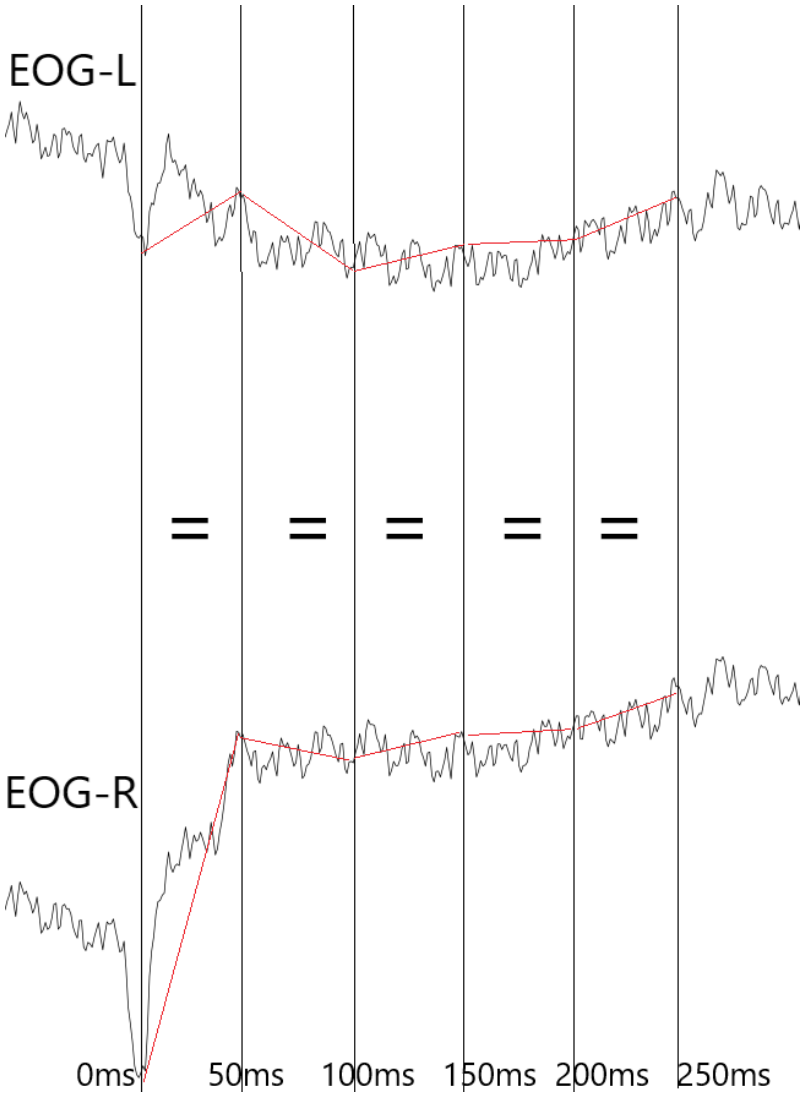


Figure 8: An segmented method to find EMs. The first Black line is the EM and the next 5 black lines indicates a point 50ms away from last line. This is done to find the red lines that shows the slope in that segment. The hope what that an EM had at least 2 of these 5 slopes in opposite directions indicating an EM. But as shown in the image this is not the case.

A new method to avoid the problem with the negative spike at the onset was needed. The slope check was moved to 21ms before the onset and lasted to 50ms after the onset to combat this problem. Now it is only one slope that is checked, and it is only accepted if one channel goes down by more than 8 microvolts while the other goes opp by more than 8 microvolts. This method did satisfactory on the EM shown in figure 8 but it did not work on some other EMs. The problem now was that sometimes the spike of the EMs starts 50ms after the onset. An example of this delayed or asynchronous start can be seen in figure 9. In this figure, the EM is marked by a green vertical line. The black vertical line is marked 50ms after the EM onset, and the red line indicates that the EOG-r channel (the top channel) has roughly the same value at the EM onset as it has 50ms after the EM onset. To avoid this problem, the endpoint of 50ms after onset was moved to 80ms after onset. All EMs inspected had the spike before 80ms after the onset, so this method was much better. With this increase in time for the spike, the amplitude criteria needed to be more. By visual inspection, 14 microvolts were chosen as all EMs moved at least 14 microvolts in 101ms. This means that the slope between 21ms before onset to 80ms after onset needs to be greater than $14/0.101 = 138.6$ microvolts per second for both EOG channels.

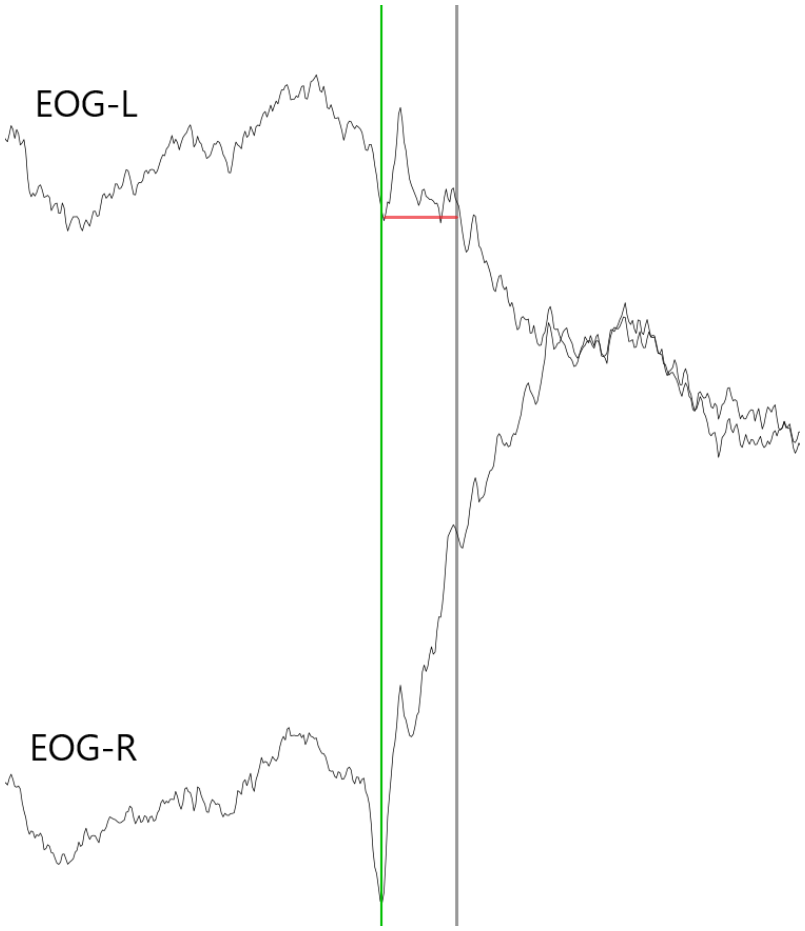


Figure 9: Unsyncronized starting point of EOG-l and EOG-r. The green line shows the onset of the EM. The gray vertical lines shows 50ms forward in time. There is no jump between onset and 50ms forward in the EOG-r channel (the channel on top)

3.4 Power spectral density criteria

After running the algorithm on a full night of sleep, it showed that it marked many EMs outside the REM sleeping stage. Investigating these EMs lead to the implementation of a Power spectral density (PSD) criteria. An image of one subject's night of sleep with the sleep stage REM and the EMs is shown in figure 11. Because of the high amount of EMs classified outside the REM sleep stage, a method using power spectral density was tested. Because visual inspection of the EM points outside the REM sleeping stage showed that muscle movements triggered them. These muscle movements are recorded with EMG channels to use for noise filtering later. When the muscle movements are active, the EMG-c channel contains a higher amount of high-frequency waves. Finding the amount of the high-frequency waves is done by finding the power spectra density (PSD). The EMG noise has a frequency of around 50 to 100 Hz, while the channel in the normal REM sleep stage has low power in the same frequencies. This is why looking at the PSD of the EMG-c channel for 55 to 95Hz should give different results in correct EM points and false EM points. An example of this can be seen in figure 13. The bottom two images show a correct EM with the EOG raw data and the PSD of the EMG channel, and the top two images show the EOG channel at an incorrect EM and its EMG channels PSD. The red line indicates the mean value of the PSD from 55 to 95Hz. The mean value of the wrong marked EM is about 4, while the actual EM has a mean value of about -15.

So to implement this method, calculation of the PSD of the EMG-c channel from 5 seconds before the EM to 5 seconds after the EM is done. Then the mean of this period is calculated and

converted to a logarithmic scale. The conversion to a logarithmic scale makes it easier to find the value differences between real and false EMs. An image of the logarithmic values over all EMs in subject s248 is shown in figure 10. This image shows that the first and last EMs have a value between -10 and 7, and from figure 11 it can be seen that the first and last EMs are outside the REM sleeping stage. This is why the criteria are set to -11 and therefore removes all the EMs at the start and absolute end of the night. Plotting the EMs after rejecting all the EMs with too high PSD value gives the results shown in figure 12. Comparing the two images of EMs found in the subject's night of sleep, it is no doubt that the PSD method worked for removing many of the wrongly placed EMs. The biggest difference in this subject is the start of the night, where the subject possibly moves his eyes before getting into a deep sleep, and at the end of the night, he wakes up and starts moving his eyes.

An overview of the step the complete algorithm takes is shown in figure 14. The figure shows all the steps the algorithm does to find the onsets.

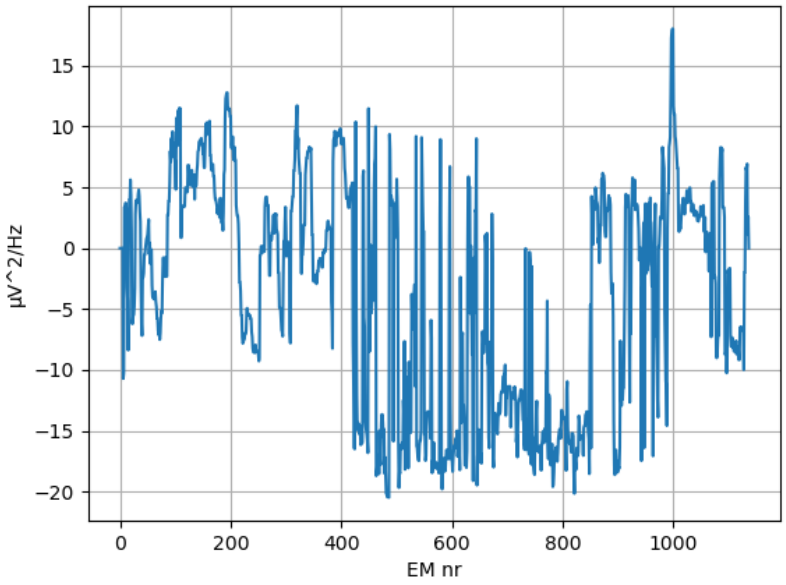


Figure 10: Logarithmic values of the PSD of all EMs in subject s248

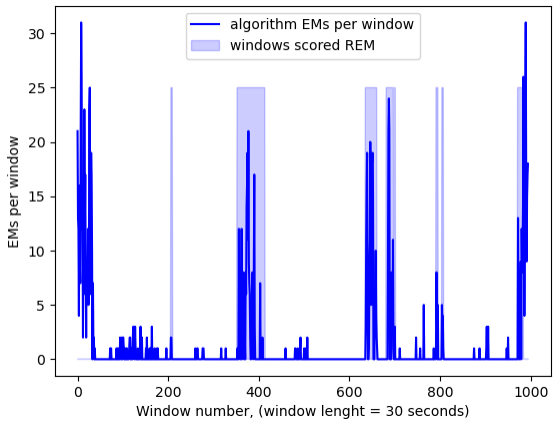


Figure 11: EM algorithm run on a full night of sleep showing how many EMs it found in every window of 30 seconds

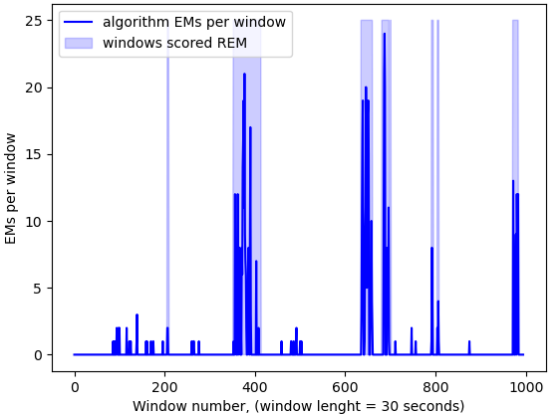


Figure 12: PSD check on EMs run after the EM algorithm had run on a full night of sleep showing how many EMs it found in every window of 30 seconds

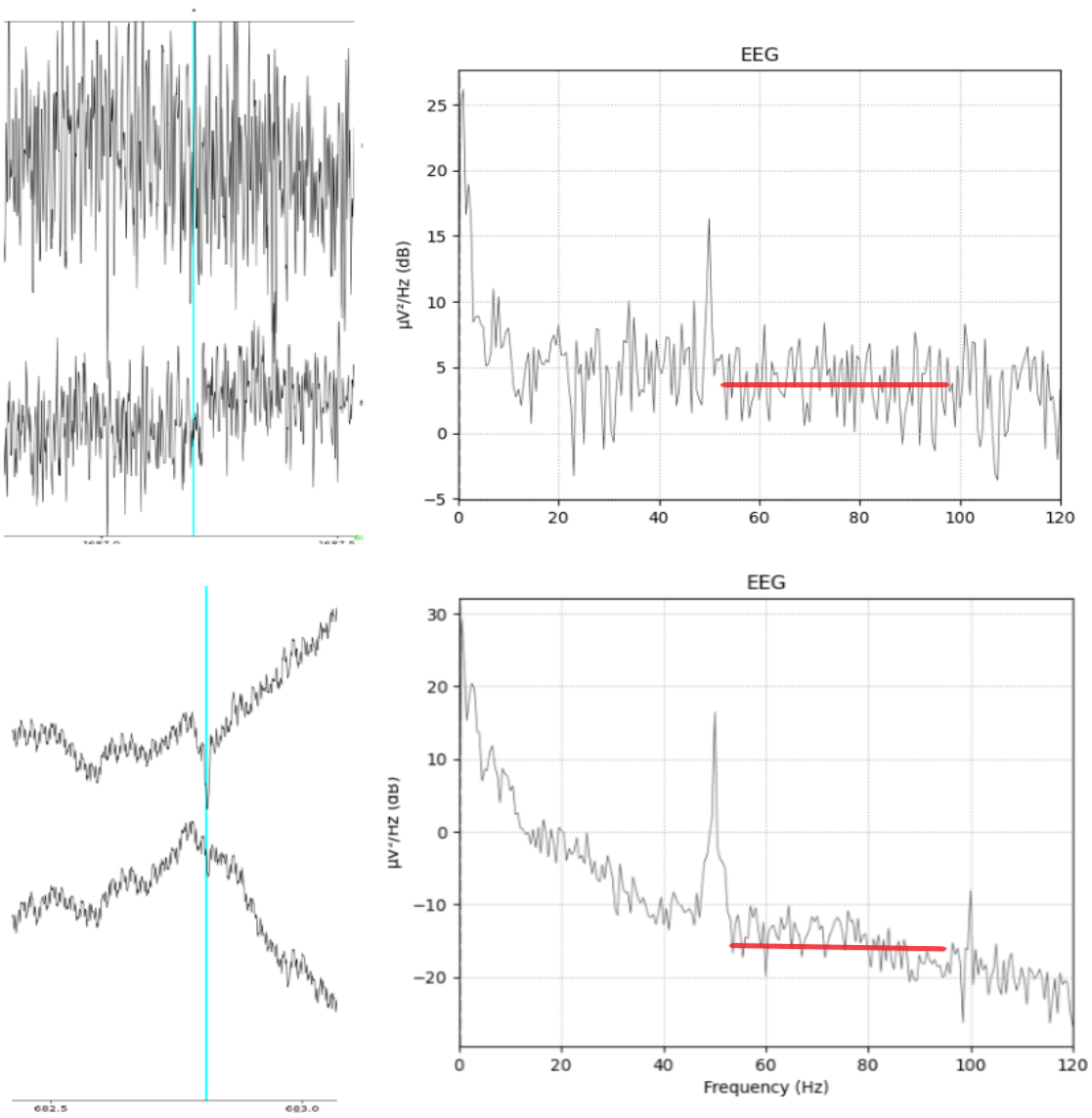


Figure 13: Power spectral density (PSD) of actual EM in REM stage (botton) vs PSD of a wrongly marked EM outside the REM stage (top). Image on the left shows the raw data of the EOG channels while the image on the right shows the PSD of the EMG channel in the same time period. The red line in the PSD shows where the mean was taken(55-95hz) and that the mean of the wrongly marked EM is around 5 micro volts squared per hertz while the actual EM has an mean of about -15 micro volts squared per hertz.

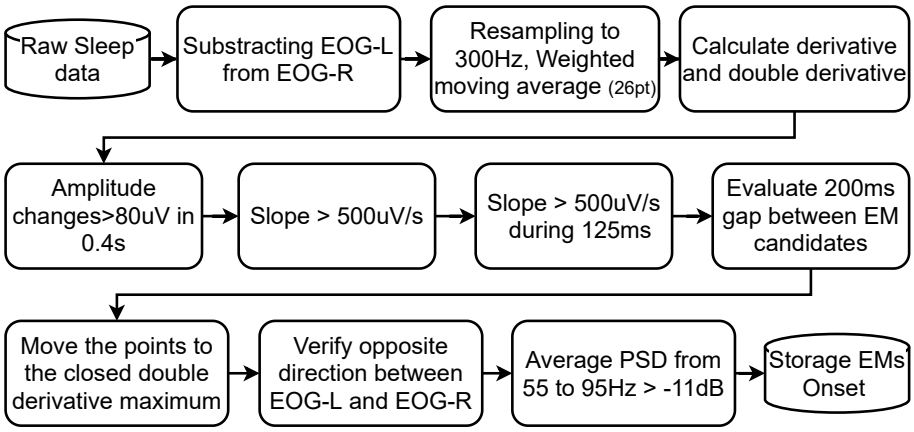


Figure 14: Overview of the complete algorithm

3.5 Algorithm performance

To evaluate the performance of the improved algorithm, the following performance measures are used: Precision, Recall, and the F1-score. Precision is the ratio of correctly predicted positive observations to the total predicted positive observations. In this case, how many of the positively rated EMs are correct. Recall or Sensitivity is the ratio of correctly predicted positive observations to the actual correct observations. In this case, how many of the actual positive EMs are rated positively. Combining these two parameters gives us an F1 score, which is the weighted average of Precision and Recall. Therefore, this score takes both false positives and false negatives into account. F1 shows how precise the algorithm is overall. The formulas for these parameters are:

$$Precision = \frac{TruePositive}{TruePositive + FalsePositive}. \tag{1}$$

$$Recall = \frac{TruePositive}{TruePositive + FalseNegative}. \tag{2}$$

$$F1 = 2 * \frac{Precision * Recall}{Precision + Recall}. \tag{3}$$

All three parameters are between 0 and 1, where 0 is the lowest performance, and 1 indicates perfect precision and recall. The reason for choosing these parameters is because they avoid the significant bias in EM marking. The bias comes from the number of possible points compared to the number of actual points, as these parameters do not use the number of true negatives.

In this study, an EM point is marked as a true positive if it is less than 0.05 seconds away from the professionally marked points. A statistic of how close the average true positive is from the professional marked points is presented in the results part.

3.6 Result of NREM

The algorithm was tested on one subject in the awake state to see if it could be used in awake state eye movements tasks as well as in sleep. This shows that the method used can be improved and used in other tasks than REM EM finder. On this awake subject, the algorithm got a Recall score of 0.86, a precision of 0.76, and an F1 score of 0.8. The average distance between algorithm-marked onsets and expert marked onsets was 13.5ms.

3.7 Result of REM

The performance of the EM onset algorithm is found by comparing the algorithm found onsets with sleep experts manually placed onsets. This manual process takes a long time, and therefore are not all subjects tested yet. The results of the eight subjects can be seen in table 2. For a point to be considered true positive, it needs to be closer than 50ms away from the corrected point. The D column in the table shows how long away the average point was from the corrected points in true positive.

Subject	TP	FP	FN	Recall	Precision	F1	D
s129	44	10	6	0.88	0.81	0.85	7.5
s240	389	97	4	0.99	0.8	0.89	5
s241	361	151	3	0.99	0.71	0.82	6.4
s242	481	154	1	1.0	0.76	0.86	7.37
s243	107	168	4	0.96	0.39	0.55	8.49
s247	595	162	12	0.98	0.79	0.87	5.34
s248	168	115	4	0.98	0.59	0.74	5.45
s300	518	367	40	0.93	0.59	0.72	8.49
Sum	2663	1224	74	0.97	0.69	0.80	

Table 2: Algorithm performance on 4 subjects over a full night of sleep. TP is true positive, FP is false positive and FN is false negative. The D is the average distance between corrected point and algorithm point in true positive.

3.8 Discussion

3.8.1 Comparison between the two algorithms

There are two significant differences between the base algorithm and the new method. The first difference is the method the algorithm uses to find points to check for the criteria. The base algorithm uses the double derivative to find these points, while the second checks all points first. This difference makes the first algorithm much faster but much more sensitive to noise. The base algorithm also tends to misplace some of the EM points because of the picking method. For example, if it is a noise spike before an EM, the first algorithm will set the noise spike and the actual EM spike as points, and if close points are removed afterwards, the real EM will be removed. In contrast, the improved algorithm will accept the same 2 points and remove the correct EM, but afterwards move the noise point to the EM start later on in the algorithm.

The second big difference is that the improved algorithm checks the EOG-L and EOG-R channels individual spikes. This check makes sure that an EM is not triggered by only one of the channels spiking. A spike in one of the channels can be due to muscle movements which are considered noise. The algorithm also checks that the spikes are in opposite directions. An opposite direction spike is essential as the EM triggers the channels to move in opposite directions, while other movements such as heartbeat cause spikes in the same direction. Both these differences make the second algorithm slower but much more reliable and precise.

3.8.2 Algorithm performance

Looking at the table 2 the false negative almost zero, and therefore are all the recalls close to perfect. This is excellent results because it is much easier to improve the algorithm when it is not a mix of missing points and false detecting points. Because of this satisfactory recall, the algorithm can be improved by setting the criteria higher to filter out more false positive points while still maintaining a low amount of false negative. Reducing the number of false positives by setting the criteria higher will lead to better precision and a better F1 score. It is also better to have high recall and bad precision than the other way around if the algorithm is used before a

manual detection is started. Having almost all true EMs marked before starting the detection, a sleep expert can look at the marked points and remove the points that are not EMs. This process is much shorter than looking for EMs without any marking beforehand.

The worst subject is the s243 that has more false positive than true positive. That subject had a bad EMG-c channel that was used in the PSD test, so instead of using the EMG-c channel, EMG-r was used. This may be the reason subject s243 is much worse than the rest of the subjects. Subject s248 and s300 also have a bad precision compared to the rest. It can be due to the subject's behavior and movement in the REM sleeping stage and should be investigated further. Setting the criteria for individual eye movement even higher might give excellent results in some subjects while making the algorithm worse for other subjects. This is why any change of the algorithm should be tested on as many subjects as possible. Looking at the sum score of the subjects combined, an F1 score of 0.8 is satisfactory. Because of the low amount of false negative points expecting the F1 score to go up a substantial amount after setting the criteria higher is a reasonable expectation. And when taking into account that false positive points are easy to check and remove manually gives this algorithm a very promising potential to increase the amount of research done on EMs in REM sleep.

The table 2 also shows the average distance the algorithm points were away from the expert marked onsets. The maximum distance being 8.49 milliseconds of the onset is a small distance. As high time precision is important when averaging the onsets to get sufficient results, this result is also promising and can be improved by learning more details of the eye movement.

The algorithm was also used in [39] and in [40]. In [39], the algorithm was used to help speed up the process of finding EMs in REM sleep. The algorithm was run on all the REM marked data to find EMs, and afterwards, the EMs was visually checked by a sleep expert. The sleep expert moved and removed points that were not EMs and mentioned that the algorithm helped with the process. It is from this project the corrected EMs were obtained and then used for calculating the algorithm performance. [40] is a paper that was made as a result of this thesis work. This paper is now under revision, and is to be published at 11th IFAC Symposium on Biological and Medical Systems.

Because of the time consuming method of find the EM onsets manually, as is done today, the algorithm can have an important impact in sleep research. It is reasonable to believe that more studies on the EM onset topic will be done in the future because of the new available method of using an algorithm do precisely find the EM onsets instead of manually doing it.

4 Scoring of REM

In this section will the method, results, and discussion of scoring REM sleep stage be presented. The section starts by explaining automatic and manual REM sleep stage scoring. Then problems with EM markings outside the REM sleeping stage are discussed before showing the results. Lastly, the results are discussed.

4.1 Automatic REM classification

When the EM detection algorithm was under development, it was tried on a full night of sleep. The results were very promising and therefore further investigated. Finding the REM sleeping stage with an algorithm would make the process of sleep analysis faster. The method used now for sleep stage classification is to visually look at a time period of 30 seconds and rate the period based on the criteria of the AASM [41]. This method uses sleep waves explained in section 2.3 together with the EMG-chin to find the sleeping stage. As the sleep period of one night is about eight hours long, 960 periods of 30 seconds epochs needs to be rated. This takes about a day to do, depending on how fast the sleep expert can rate sleep data. Using the algorithm made for EM detection on a full night of sleep takes about 10 minutes. In addition to taking many hours less time, the researcher can do other activities while the algorithm runs. This speed increase, together with the possibility to find sleep stages without needing a sleep expert, is the main advantage of using the algorithm to rate sleep data. The main disadvantage is that the algorithm is less precise than a sleep expert is, and the algorithm will not find REM sleep stages that do not have EMs in them. The algorithm also does not find the exact start and stop timing of the REM sleeping stage.

4.2 EMs outside the REM sleeping stage

Using the algorithm on a full night of sleep, shown in figure 15 shows that it finds EMs outside the REM sleeping stage. Because the algorithm finds EMs outside the REM sleeping stage, it is hard to know exactly when the REM sleeping stage is from looking at the algorithm results. All epochs that have more than 3 EMs in them are in the REM sleeping stage for this subject. This can vary from subject to subject but is a baseline to find where the REM sleep stage is. Epochs with one or two EMs marked should not be considered REM sleep stage unless it is between epochs that have a high number of EMs marked. The algorithm uses PSD to remove the EMs made by muscular movements. However, this method did not remove all EMs outside the REM sleep stage. In section 3.4 an explanation of how the power spectral density was used to remove some wrongly pleased EMs. Because this technique did not remove all EMs outside the REM sleeping

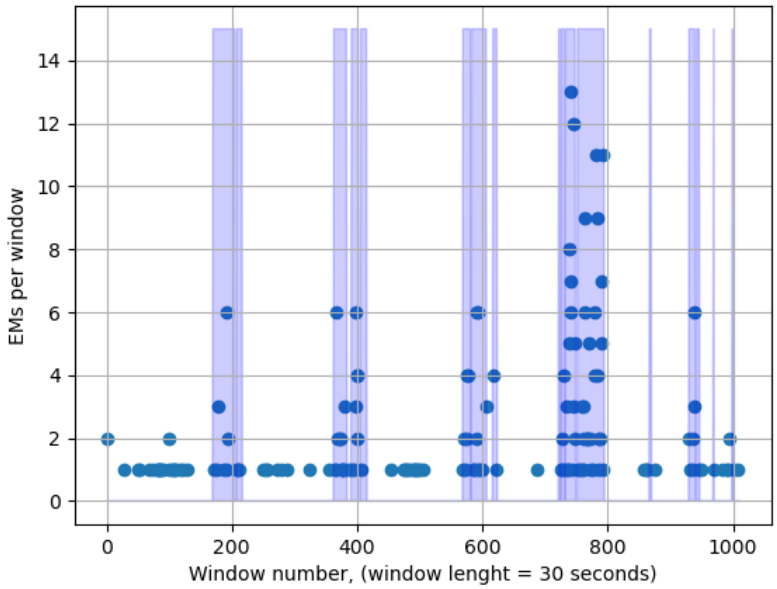


Figure 15: Shows the full night of sleep of subject s248, the blue dots shows how many EMs the algorithm found in the epoch, and the blue boxes shows where the REM sleep stage is.

4.3 REM sleep stage finding results

Using the algorithm on a full night of sleep and plotting the comparison of EMs detected to the REM sleep stage categorized by sleep experts is done. In this subsection, only two subjects are presented. The rest of the subjects except s243 can be found in the appendix A. Subject s243 had a bad EMG channel that prevented the PSD method from working. The two subjects selected to be presented are subjects s129 and s241. These are chosen because s129 shows some of the problems with the method while s241 shows the best result.

Figure 26 shows how many EM points the algorithm found for subject s129 in each window compared to the expert rated sleep stage REM. The method of rating the sleep stage is by looking at 30-second windows and categorize them. This is why the x-axis of the figure is in 30-second windows. The figure shows that the algorithm found many points in between window 0 and window 20. This comes from eye movement the subject does before he fully submerges into sleep. The figure also shows that the algorithm finds many single EMs in the windows between 150 and 400. After window 400 are most of the EMs found are in the REM sleep stage. Except for the night's start are all windows that the algorithm found more than 5 EMs in them, in the REM sleep stage. Ideally, should the algorithm only mark EMs in the REM sleep stage and all the other marked EMs indicate potential improvements.

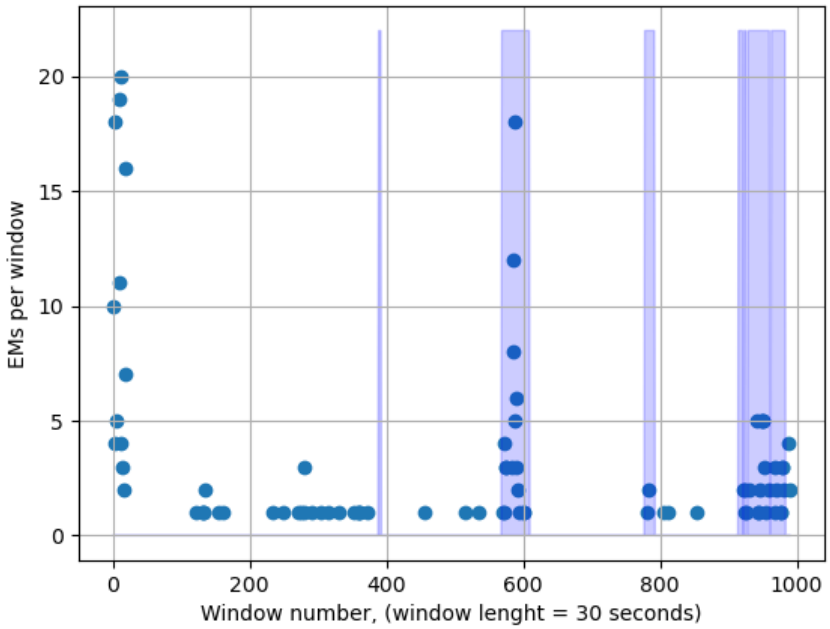


Figure 16: EMs found by algorithm in window comapired to sleep expert rated REM sleep stage for subject s129

Figure 28 shows subject s241 full night of sleep. This subject shows much more promising results than s129. The algorithm has managed to avoid marking a substantial amount of wrong EMs at the start of the night. It is only two short periods outside the REM sleep stage that are marked, and in these two periods, no window has more than two markings in it. While in the REM sleep stage, the windows have up to 23 EMs showing a clear difference in marking between in REM sleep stage and outside it. This subject also has EMs in all the REM sleep stages.

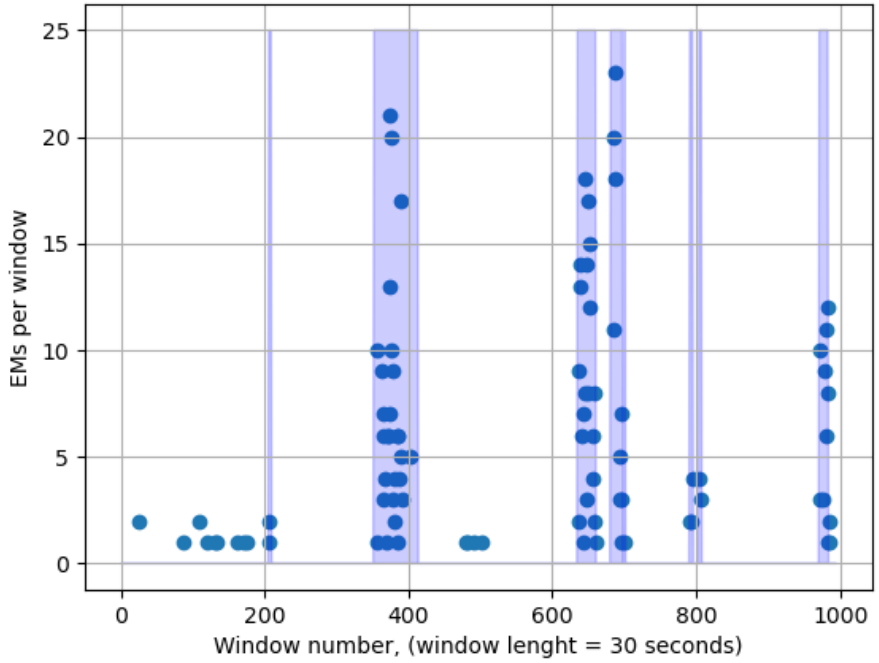


Figure 17: EMs found by algorithm in window comapired to sleep expert rated REM sleep stage for subject s241

4.4 Discussion

The figures shown in section 4.3 and in the appendix A shows that finding the REM sleeping stage with the algorithm is possible but needs more work. Firstly do the results vary a lot from subject to subject. And therefore, it is hard to trust the results without any other test or control checks. Secondly, there are REM sleep stage periods with no EMs in them. This makes it impossible to find with this algorithm. And lastly, it is hard to know the exact starting point and ending point of the REM sleep stage with this algorithm. For most subjects, it is easy to see where the REM sleep stage is but not the exact starting point or endpoint. For example, looking at 28, if the blue indication of the REM sleep stage is taken away, it will be tough to know if it is one long period at about window 800 or if it is two shorter ones.

With the algorithm as it is now, it can be used as a heads up to the sleep experts before they categorize the sleep. This will make the job easier because they know where there should be some REM periods and where they should not be. Or the algorithm can be used together with other sleep categorizing algorithms to get better results. The sleep categorizes algorithms that exist now is bad at finding REM sleep as it contains most of the frequencies the other sleep stages contains and therefore can be similar to the other sleep stages.

As it is the same algorithm that is tested in section 3.8.2 it is known that it counts too many EMs. As suggested in that section, making the criteria higher might improve the algorithm for finding the REM sleep stage also. It is reasonable to expect some or all of the wrongly marked EMs outside the REM sleep stage to be removed with higher criteria. The PSD criteria are also something that should be considered improved. As the criteria is now at -11 microvolts squared per hertz, it should be further investigated what the best value for this criteria is. As seen in figure 13 this value works fine with the extreme cases, but in this study, the PSD effect is only looked at and regulated for two subjects. As the figure 26 shows many wrong EMs at the start of the night, it should be investigated why they are not removed with this PSD criteria. A baseline of the EMG-c channel can be found at the start of the night (the first 10 windows) and used to find the best criteria value for the PSD filter. Also, visual inspection of the PSD of the EMG channel in more subjects can lead to a better understanding of the criteria value.

5 Source Localization of Pre-REM brain activity

This section presents the steps taken to obtain source localization of pre-REM negativity. The section starts by presenting the filtering and prepossessing needed. Then the models are calculated, and two methods of source localization are presented. Afterwards a t-test is done to find significant activation, and the results are presented. Lastly, the results are discussed

5.1 Method sLORETA

sLORETA is a method used in the inverse problem of source localization. Different methods are used for different purposes and are focused on different things. Among these focuses are minimum localization error, less complexity, and more validation. As the inverse problem has many solutions, there is no consensus among the EEG researchers which method is the best to use. The sLORETA method is made to be better at finding deeper sources, [42] and the reason for choosing this method is to be able to compare with the study [19].

5.2 Filtering and preprocessing the data

Before computing the models, the data needs to be pre-processed to get the best results. Reading the dataset is done by using the method `mne.io.read_raw_bdf()`. This method takes in the filename and location of the dataset and makes it accessible by a variable in python. Storing the full dataset in a variable can overload the computer's memory, so preload is set to false to avoid this problem. To make the data set easier to work with, the channel names are changed to the standard names going from A1-A32, B1-B32, C1-C32, D1-D32. An image of the sensor names and positions can be seen in figure 18. Then the channels that are not the EEG channels, the EMG and EOG, are set to be channel types EMG, EOG, and misc, respectively. This is done with `raw.set_channel_types` and prevents the channels from interfering with the source localization. Afterward, the electrode positions together with the head model are set up. In this paper, a template head model is used. The template head model can lead to errors in further calculations, but an MRI of the patient was not available. The template head model used is the "fsaverage". "Fsaverage" is a model provided by FreeSurferWiki [26]. The model is constructed by using many MRIs to find the average position of components in the head. The head model "fsaverage" with electrodes is plotted in Figure 19. The red points on the scalp of the head are the electrodeposition loaded from the biosemi128 standard positions setup. And the yellow points inside the head are the possible brain activity points. Biosemi128 is the electrodeposition used when recording the data set in this study. Biosemi128 is a standard electrode setup and can be seen in the Figure 18. The figure shows the head with the sensor placement seen from above. Furthermore, the EEG channels reference is set to average. This makes the values of the sensors closer to zero and makes all the sensors have the same reference. This average reference is needed for computing the inverse model later on.

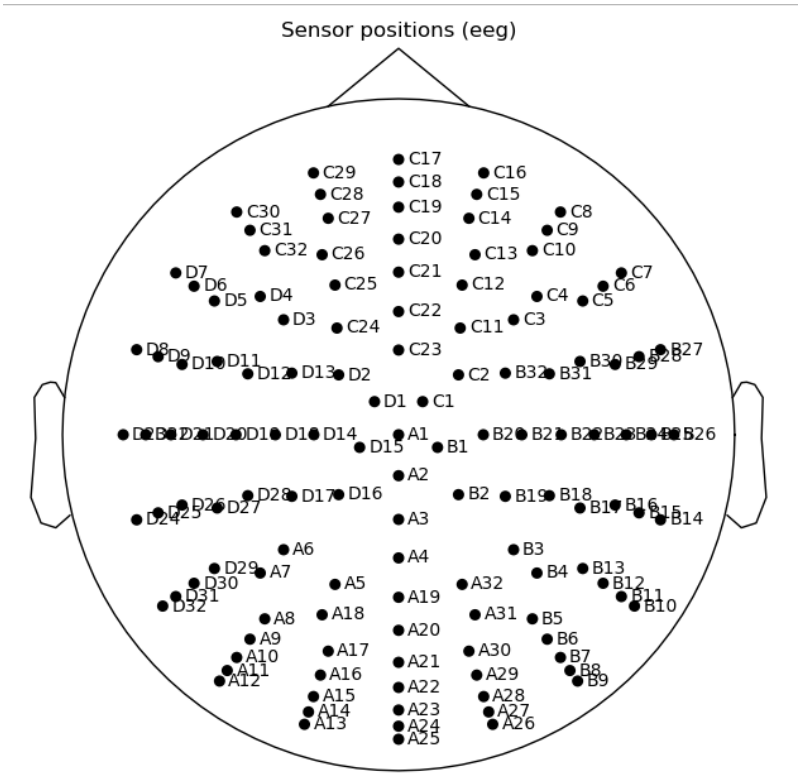


Figure 18: Sensor positons of biosemi128 setup, and names of the sensors

Before filtering the data, it is cut 10 seconds before and after each EM to avoid long and unnecessary filtering time. Filtering the data between 0 and 300Hz with a high pass and low pass filter. This is done to avoid unnecessary noise in the channels. A notch filter is also implemented at 50Hz because that is the frequency of the power grid where the data was recorded and therefore affects the data.

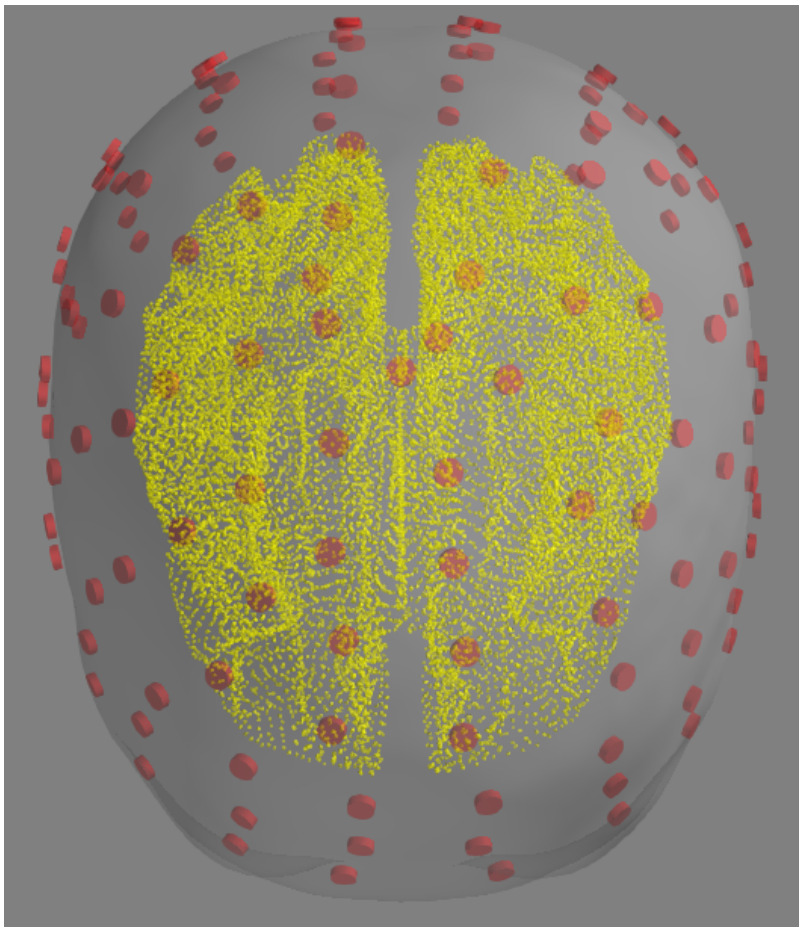


Figure 19: Head model seen from above, where red dots are electrode position and yellow dots are possible brain activation points

5.3 Computing the models

The forward model, covariance, and inverse operator need to be calculated before source localization can be done. To compute the forward model, the function `mne.make_forward_solution()` is used. This function needs to know the head model and the dataset. It is important to set the correct sensor position in the data set before using this method. This is because the method uses the sensor positions to calculate the forward model, and the results will not be correct without it. This setup is explained in 5.2. After calculating the forward model, covariance is calculated. To calculate the covariance, a time period of 4000 seconds in the N1-N3 sleep stage is used. The calculation is done with the function `mne.compute_raw_covariance()` and only needs the data for the 4000 second time period. The inverse operator is calculated by using the function `mne.minimum_norm.make_inverse_operator()`. This function needs to know the noise covariance matrix between the electrodes and the forward model. When the inverse operator is calculated, it is used to find source activation in the brain.

5.4 Source localization of EM onsets

Finding the activity in the brain starts by making the epochs. Epochs are made by taking raw data and cut it 200ms before the EM onsets to 50ms after the EM onset for all EMs. Then a baseline is used on the epochs from 200ms to 150ms before the onset. This is done to move the different channels around 0 volts. This is important to do as it makes the channels have an equal effect on the source localization. Afterwards, are the epochs averaged, making an evoked object. The evoked object looks like figure 20 and a spike at 0 seconds (the onset) can be seen. From here,

two different methods of finding significant brain activity are done. The differences in the methods come from when to average the time span of pre-REM and baseline. The first method averages the evoked objects, while the second method averages the source activation points.

The first method of averaging the source activation is explained. In this method, after finding the evoked object, the inverse operator found in 5.3 is applied to the evoked data. This calculates the brain source estimates. Source estimates hold the activation value for every point in the brain. This means that it contains a 2D array with the shape 20484x256. It is 20 484 brain activation points seen as yellow dots in figure 19. The 256 comes from the time points available (-200ms to 50ms) multiplied by the sampling points per millisecond (1024/1000). Then the brain activation for each point is averaged over two time spans. The first time span is the baseline time span, and this time span is between 150ms before onset to 140ms before onset. Then finding the mean value in this time span for every brain activation point (20 484) and save it as a baseline source. After the baseline is calculated, the pre-REM time span is next. This time span is between 150ms before onset to 20ms before onset. The same procedure with finding the mean value for each activation point in this time span and save it as a pre-REM source. After finding the baseline source and the pre-REM source for all eight subjects, the data are ready for the T-test.

The second method finds the mean value of the time spans in the evoked object instead of the source estimation. This means that after finding the evoked object for a subject, the evoked object is averaged between 150ms before onset to 140ms before onset, giving an evoked baseline object out. The same process is done for the pre-REM object between 150ms before onset to 20ms before onset. Then the inverse operator is used on the baseline evoked and the pre-REM evoked, giving two source estimates with an array shape of 20 484 x 1. After this is done on all eight subjects, two arrays of 20 484x8 are ready for the T-test.

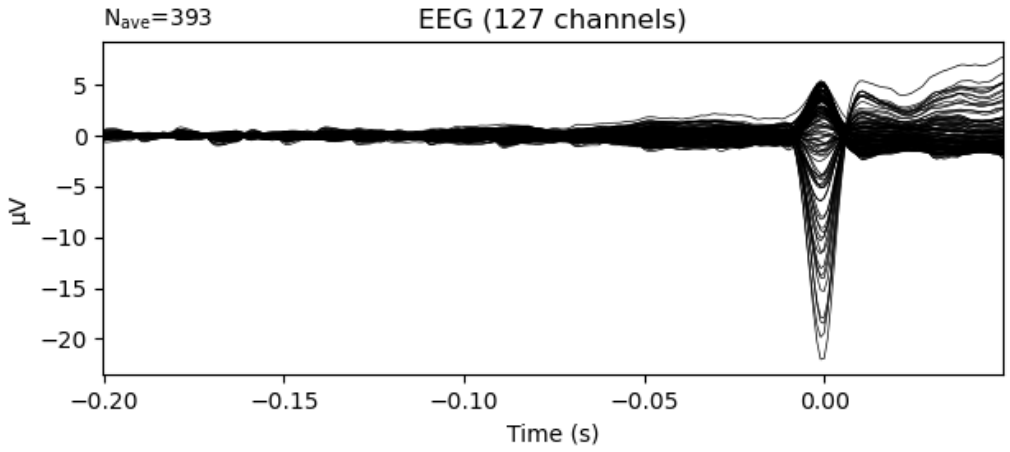


Figure 20: Evoked plot of subject s240. Showing the spike at the EM onset for the different 127 channels. Nave=393 means its 393 epochs that is averaged to get this plot

5.5 T-test to find significant brain activity

After finding the source estimates for the baseline and the pre-REM, t-tests are calculated. Calculating the p-value between the two conditions is done to find the brain activation points that are significantly different between the pre-REM period and the baseline. This t-test is done on all the 20 484 brain activation points, and all the points with a p-value of less than 0.05 are considered significant. The significant brain activation points are saved as value 1, while the others are saved as value 0. Then the source activation is plotted, showing the points on the head model. The brain atlas is also plotted on the head model. A brain atlas is a grouping of the different regions in the brain. An image of the brain plotted with the brain regions is shown in figure 21. In this figure, the brain regions are shown with their unique color.

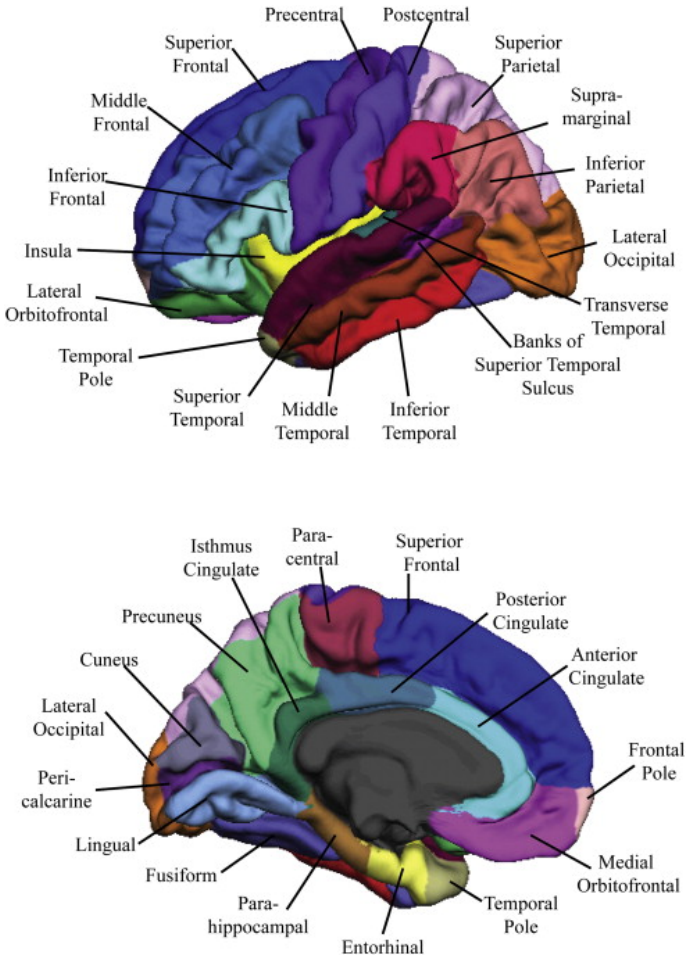


Figure 21: Brain atlas, shows the separated brain regions. [4]

5.6 Results from Source localization on EMs

Figure 22, 23, 24, and 25 shows the significant sources found by using t-test between pre-REM source activation and baseline source activation. The red spots marked on the brain plots are the activation places, while the white is where it was no significant difference between pre-REM and baseline. The labels are also printed on the surface of the brain as colored lines around the label places.

5.6.1 Brain activation averaged

Figure 22 shows the brain plots from the lateral side, which is the brain seen from the side, and from the medial side, which is a cross section of where the left and right hemispheres meet. As the figure shows, it is more activity on the medial side of the brain than the lateral side. The densest red markings are in the middle of the brain, in the regions near the thalamus and striatum. Due to the structure of the thalamus and striatum, it is consider that they do not produce EEG potentials or their influence in the EEG signal itself is null. The lateral part has the most activity in the lateral orbitofrontal and the upper superior parietal. The left hemisphere has more activity in the lateral part compared to the right hemisphere. Still, the right hemisphere has more activity in the medial part compared to the left hemisphere.

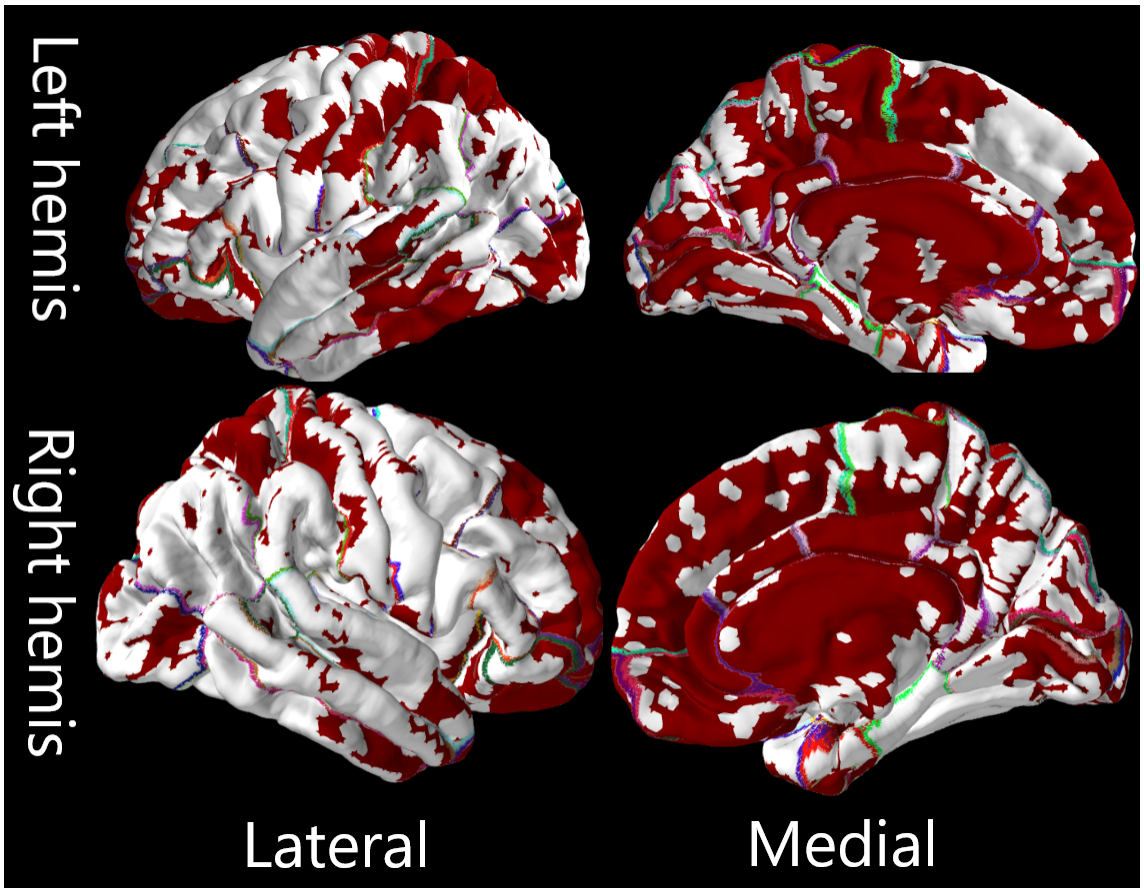


Figure 22: Significant source activation shown from the lateral and medial view

Figure 23 shows the brain from the dorsal and ventral views. Dorsal is viewed from above the head, and ventral is from underneath the head. Both models have the front of the head facing down as they are looking at the figure text of the image. The image shows that the densest activation area is in the front of the head in the ventral view. There is also some activation in the postcentral and precentral brain regions.

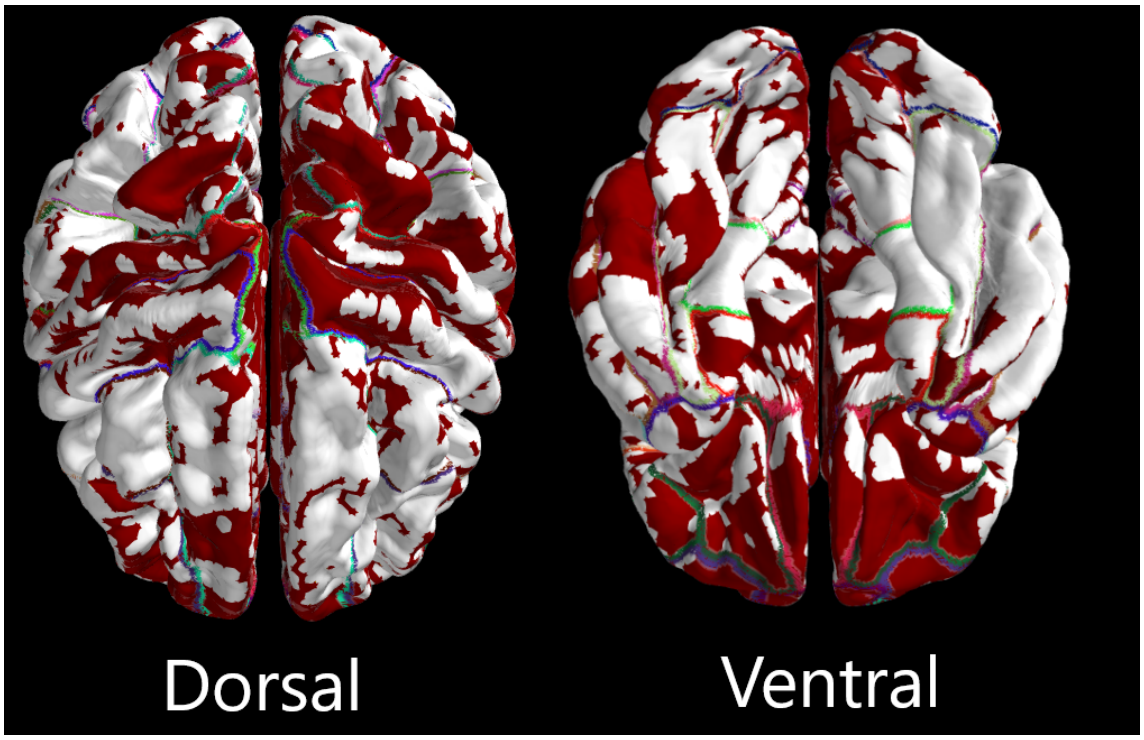


Figure 23: Significant source activation shown from the dorsal and ventral view

5.6.2 Evoked averaged

Figure 22 shows the lateral and medial view of the brain activation using the method of averaging the evoked object instead of the source activations. It is a lot less statically significant activation points than the method of averaging the source activation. Almost no clear regions on the lateral part of the brain are marked in red. Some activation can be seen in the lateral orbitofrontal regions and the postcentral regions. The left hemisphere also has some activation in the precentral region and the inferior temporal region, but these are less dense. The medial part of the brain still has the most activation near the striatum regions. The left hemisphere also has a small amount of activation in the paracentral and posterior cingulate regions.

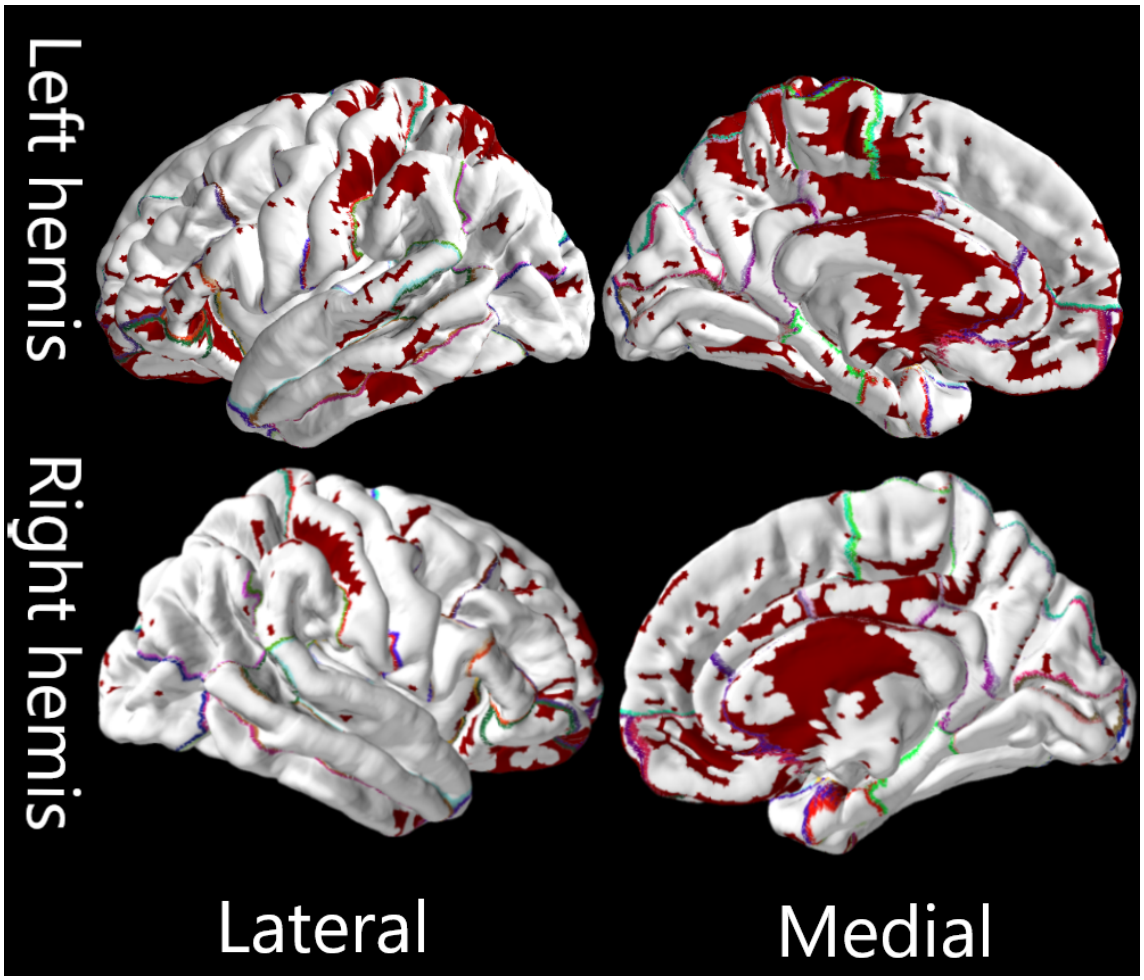


Figure 24: Significant source activation shown from the lateral and medial view

Figure 23 shows the dorsal and ventral views of the brain with most activation in the front of the head in the ventral view. These is the medial orbitofrontal and the temporal pole regions.

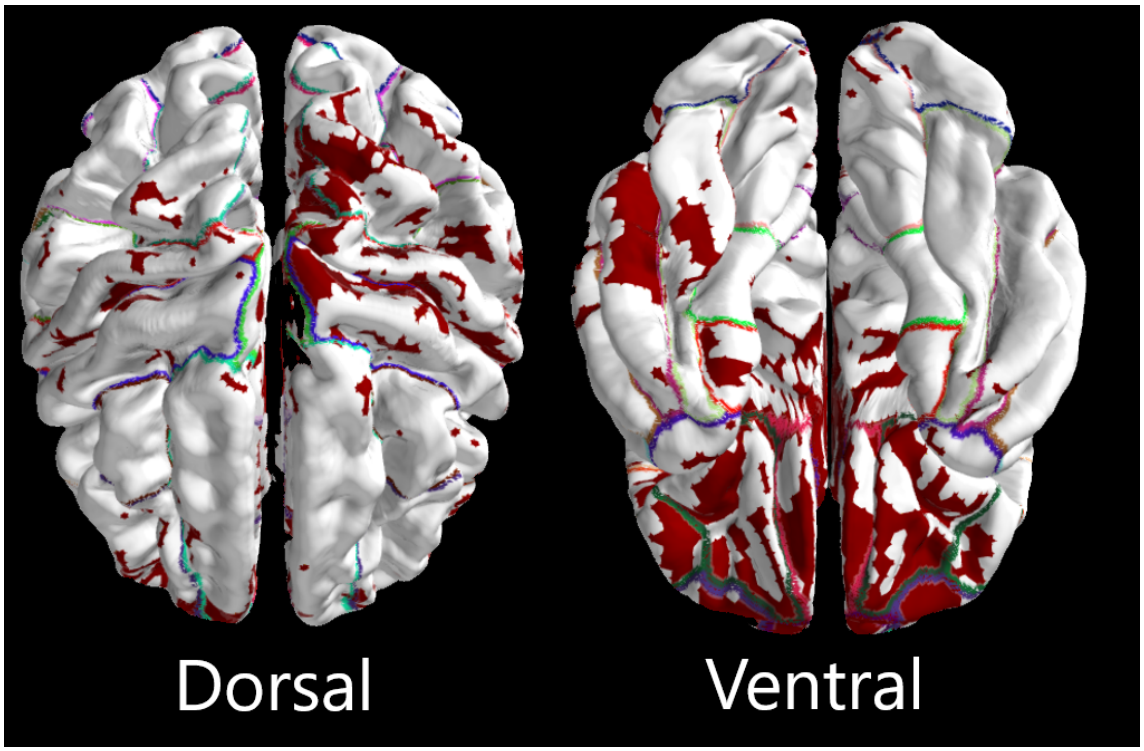


Figure 25: Significant source activation shown from the dorsal and ventral view

5.7 Discussion

Both methods used in this paper were based on eight subjects, however, to obtain cleaner results, it is recommended to involve more subjects However, the t-test is still valid with a small sample size as explained in [43]. Brain activity related to onset of EMs is researched before in studies [19, 20], however both these studies are done with LdEEG while in this study is used.

The two methods shown in this paper had a considerable difference in the result. The method averaging the brain activation had a higher number of significant sources than the method averaging the evoked object. This comes from the inverse operator differentiating major differences less than small differences. The source activation averaged has then many small differences in the source activation, and summing these up gives a bigger difference than using the inverse operator on a big difference that is already summed up. The source activation places in the evoked object averaged method still have activation in the same regions as the brain activation averaged, but smaller area. The method used in the study [19] is the averaging the evoked object method, but the method averaging the brain activation gives results that resemble the study's result more. This can be due to differences in the subject used or because of the use of HdEEG instead of LdEEG.

5.7.1 Brain activation averaged

The brain activation averaged method results showed that the regions near the striatum had the most significant activation of the brain in pre-REM negativity. From studies [44, 45], the striatum is connected to the reward system in the human brain. This means that the brain gets some sort of reward or punishment in the pre-REM negativity. This might be the effect that makes humans move the eyes. The study [19] also shows activation in the striatum in both hemispheres. While that study did not find as much activation as this study found in the striatum, both studies indicate that the striatum is an essential part of the pre-REM negativity.

Another region that was significantly activated was the lateral orbitofrontal region. The study [46] explains that the lateral orbitofrontal region is observed to be activated when insufficient

information is available to determine the appropriate course of action. This region is also shown to be connected to actions that require the suppression of previously rewarded responses. This indicates a connection between lateral orbitofrontal suppression of rewarded response and the striatum that controls the reward system. The lateral orbitofrontal region is also shown activated in the study [19], where it is the densest area shown.

The postcentral gyrus did also have some activation. This region of the brain is associated with the touch sensor of the body [47]. This region did not have any significant activity in the study [19]. As it is hard to reasonably link touch sensory to EMs in REM sleep, this might be a coincidence but should be further investigated.

5.7.2 Evoked averaged

The results from the evoked averaged method did also have the densest activation in the striatum regions. Because this region had the densest activation in both methods used, and it was activated in the study [19], it is reasonable to assume that this region is one of the important regions in pre-REM activation. This region is active while the brain gets a reward or punishment, which leads to the possibility that EMs in REM comes from the brain trying to reward or punish an activity in REM sleep.

The orbitofrontal and the postcentral regions did also have significant activation in this method. The orbitofrontal region is in the front of the head close to the eyes and was also activated in the other method and in the study [19] as this region is linked to decision making [48], it is natural to assume that some specific decision has to be approved before the EMs accrue. The postcentral gyrus placed on the top of the head has some activation points in this and the other method. The activation is small parts of the postcentral gyrus and indicates a specific sensory touch to be activated. Because this region did not have activation in the study [19], it might indicate a specific sensory touch related to the setup of the eight subjects used in this study.

6 Conclusion and Future work

This section presents the conclusion for the three main focuses in this paper and explains what to focus on in future work.

6.1 Conclusion

This paper had three main focuses, EM detection, REM stage scoring, and source localization of pre-REM activation. The EM detection worked very well for almost all EMs but did mark some extra points that were not EMs. Because of the extra points the algorithm marks, the results of the EM detection algorithm should be checked visually and not just blindly accepted. The algorithm did also show that it could be used as a REM stage finder. It marked almost all of the REM epochs with more than three EMs, while the NREM sleeping stages were marked with less than three EMs. However, the algorithm as it is now can not mark the precise onset and cutoff of the REM sleeping stage. Because of this problem, the best use for the algorithm as a REM finder is to give an indication to a sleep expert before the expert starts to rating the sleep, making it easier to find the REM sleeping stage. The source localization of pre REM activation showed that the most significant areas in the brain were the striatum and the orbitofrontal regions. These are the regions that control if the brain gets a reward or punishment and the brain's decision-making process.

6.2 Future work

Future work for EM detection should focus on improving the algorithm by setting higher criteria for EMs. If possible keeping the high score in recall while improving the precision, making the F1 score much better. For using the algorithm in REM sleep stage finding, the focus should be on setting specific criteria for when an epoch is categorized as REM and when it is NREM. Implementing criteria on the EEG and EMG channels in addition to the EMs found. Future work for source localization of pre-REM activity should try to study brain activation with a higher number of subjects, making the results more general and linking the results to brain diseases.

Bibliography

[1] R. K. Malhotra and A. Y. Avidan, "Sleep Stages and Scoring Technique Introduction to Sleep Stage Scoring," Tech. Rep., 2014.

[2] "File:Hypro zyklus 1 en 103.svg - Wikipedia." [Online]. Available: https://en.wikipedia.org/wiki/File:Hypro_zyklus_1_en_103.svg

[3] K. Takahashi, Y. Atsumi, T. Metropolitan Matsuzawa Hospital, and K.-m. Setagaya-ku, "Sleep and Sleep States Precise Measurement of Individual Rapid Eye Movements REM Sleep of Humans. In," Tech. Rep., 1997. [Online]. Available: https://academic.oup.com/sleep/article/20/9/743/2731668

[4] M. Jalbrzikowski, R. Jonas, D. Senturk, A. Patel, C. Chow, M. F. Green, and C. E. Bearden, "Structural abnormalities in cortical volume, thickness, and surface area in 22q11.2 microdeletion syndrome: Relationship with psychotic symptoms," *NeuroImage: Clinical*, vol. 3, pp. 405–415, 1 2013.

[5] "Stages of Sleep - Sleep Foundation." [Online]. Available: https://www.sleepfoundation.org/articles/stages-of-sleep

[6] "Electroencephalogram (EEG) - NHS." [Online]. Available: https://www.nhs.uk/conditions/electroencephalogram/

[7] I. G. Campbell, "EEG recording and analysis for sleep research," p. Unit10.2, 2009. [Online]. Available: /pmc/articles/PMC2824445/?report=abstracthttps://www.ncbi.nlm.nih.gov/pmc/articles/PMC2824445/

[8] E. K. S. Louis, L. C. Frey, J. W. Britton, L. C. Frey, J. L. Hopp, P. Korb, M. Z. Koubeissi, W. E. Lievens, E. M. Pestana-Knight, and E. K. S. Louis, "Appendix 6. A Brief History of EEG," 2016. [Online]. Available: https://www.ncbi.nlm.nih.gov/books/NBK390348/

[9] C. Gottesmann, "Discovery of the dreaming sleep stage: A recollection," pp. 15–16, 1 2009. [Online]. Available: /pmc/articles/PMC2625318/https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2625318/

[10] C. Smith and L. Lapp, "Increases in number of REMS and REM density in humans following an intensive learning period," *Sleep*, vol. 14, no. 4, pp. 325–330, 1991. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/1947596/

[11] T. Abe, H. Nittono, and T. Hori, "Current sources of the brain potentials before rapid eye movements in human REM sleep," *International Congress Series*, vol. 1270, no. C, pp. 241–244, 8 2004.

[12] T. Abe, T. Matsuoka, K. Ogawa, H. Nittono, and T. Hori, "Gamma band EEG activity is enhanced after the occurrence of rapid eye movement during human REM sleep," *Sleep and Biological Rhythms*, vol. 6, no. 1, pp. 26–33, 1 2008. [Online]. Available: https://link.springer.com/article/10.1111/j.1479-8425.2008.00332.x

[13] R. Stickgold, D. Whidbee, B. Schirmer, V. Patel, and J. A. Hobson, "Visual discrimination task improvement: A multi-step process occurring during sleep," *Journal of Cognitive Neuroscience*, vol. 12, no. 2, pp. 246–254, 2000. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/10771409/

[14] P. Maquet, J. M. Peters, J. Aerts, G. Delfiore, C. Degueldre, A. Luxen, and G. Franck, "Functional neuroanatomy of human rapid-eye-movement sleep and dreaming," *Nature*, vol. 383, no. 6596, pp. 163–166, 1996. [Online]. Available: https://www.nature.com/articles/383163a0

[15] J. C. Gillin, W. C. Duncan, D. L. Murphy, R. M. Post, T. A. Wehr, F. K. Goodwin, R. J. Wyatt, and W. E. Bunney, "Age-related changes in sleep in depressed and normal subjects," *Psychiatry Research*, vol. 4, no. 1, pp. 73–78, 1981. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/6939001/

[16] H. W. Lahmeyer, E. O. Poznanski, and S. N. Bellur, "EEG sleep in depressed adolescents," *American Journal of Psychiatry*, vol. 140, no. 9, pp. 1150–1153, 1983. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/6614218/

[17] T. A. Mellman, B. Nolan, J. Hebding, R. Kulick-Bell, and R. Dominguez, "A polysomnographic comparison of veterans with combat-related PTSD, depressed men, and non-ill controls," *Sleep*, vol. 20, no. 1, pp. 46–51, 1997. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/9130334/

[18] I. Feinberg, T. C. Floyd, and J. D. March, "Effects of sleep loss on delta (0.3-3 Hz) EEG and eye movement density: new observations and hypotheses," *Electroencephalography and Clinical Neurophysiology*, vol. 67, no. 3, pp. 217–221, 1987. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/2441955/

[19] T. Abe, K. Ogawa, H. Nittono, and T. Hori, "Neural generators of brain potentials before rapid eye movements during human REM sleep: A study using sLORETA," *Clinical Neurophysiology*, vol. 119, no. 9, pp. 2044–2053, 9 2008.

[20] K. Ogawa, T. Abe, H. Nittono, K. Yamazaki, and T. Hori, "Phasic brain activity related to the onset of rapid eye movements during rapid eye movement sleep: Study of event-related potentials and standardized low-resolution brain electromagnetic tomography: Phasic and tonic REM sleep," *Journal of Sleep Research*, vol. 19, no. 3, pp. 407–414, 9 2010. [Online]. Available: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2869.2009.00809.xhttps://onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-2869.2009.00809.xhttps://onlinelibrary.wiley.com/doi/10.1111/j.1365-2869.2009.00809.x

[21] C. Lustenberger, R. Huber, and L. J. Larson-Prior, "High density electroencephalography in sleep research: potential, problems, future perspective," 2012. [Online]. Available: www.frontiersin.org

[22] Ole Drange, "Electrode reduction in EEG sleep research," Ph.D. dissertation, NTNU, Bergen, 2020.

[23] M. A. Carskadon and W. C. Dement, "Chapter 2-Normal Human Sleep : An Overview," Tech. Rep.

[24] R. R. S. M. H. M. R. M. L. M. D. T. P. M. S. F. Q. M. M. M. T. D. B. V. V. M. f. t. A. A. o. S. M. Richard B. Berry, MD (Chair); Claude L. Albertario, "The AASM Manual for the Scoring of Sleep and Associated Events," American Academy of Sleep Medicine, Tech. Rep., 2018.

[25] D. Purves, G. J. Augustine, D. Fitzpatrick, L. C. Katz, A.-S. LaMantia, J. O. McNamara, and S. M. Williams, "Types of Eye Movements and Their Functions," 2001. [Online]. Available: https://www.ncbi.nlm.nih.gov/books/NBK10991/

[26] "FreeSurferWiki - Free Surfer Wiki." [Online]. Available: https://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferWiki

[27] R. Oostenveld and P. Praamstra, "The five percent electrode system for high-resolution EEG and ERP measurements," *Clinical Neurophysiology*, vol. 112, no. 4, pp. 713–719, 4 2001.

[28] R. Grech, T. Cassar, J. Muscat, K. P. Camilleri, S. G. Fabri, M. Zervakis, P. Xanthopoulos, V. Sakkalis, and B. Vanrumste, "Review on solving the inverse problem in EEG source analysis," p. 25, 11 2008. [Online]. Available: http://jneuroengrehab.biomedcentral.com/articles/10.1186/1743-0003-5-25

[29] C. M. Michel and D. Brunet, "EEG source imaging: A practical review of the analysis steps," *Frontiers in Neurology*, vol. 10, no. APR, 2019.

[30] S. Asadzadeh, T. Yousefi Rezaii, S. Beheshti, A. Delpak, and S. Meshgini, "A systematic review of EEG source localization techniques and their applications on diagnosis of brain abnormalities," 6 2020. [Online]. Available: https://doi.org/10.1016/j.jneumeth.2020.108740

[31] R.D. Pascual-Marqui, "Standardized low resolution brain electromagnetic tomography (sLORETA): technical details," pp. 0–16.

[32] T. K. Kim, "T test as a parametric statistic," *Korean Journal of Anesthesiology*, vol. 68, no. 6, pp. 540–546, 12 2015. [Online]. Available: /pmc/articles/PMC4667138//pmc/articles/PMC4667138/?report=abstracthttps://www.ncbi.nlm.nih.gov/pmc/articles/PMC4667138/

[33] "Statistics: 1.1 Paired t-tests," Tech. Rep.

[34] A. Gramfort, "MEG and EEG data analysis with MNE-Python," *Frontiers in Neuroscience*, vol. 7, 2013.

[35] C. R. Harris, K. J. Millman, S. J. van der Walt, R. Gommers, P. Virtanen, D. Cournapeau, E. Wieser, J. Taylor, S. Berg, N. J. Smith, R. Kern, M. Picus, S. Hoyer, M. H. van Kerkwijk, M. Brett, A. Haldane, J. F. del Río, M. Wiebe, P. Peterson, P. Gérard-Marchant, K. Sheppard, T. Reddy, W. Weckesser, H. Abbasi, C. Gohlke, and T. E. Oliphant, "Array programming with NumPy," pp. 357–362, 9 2020.

[36] W. McKinney, "Data Structures for Statistical Computing in Python," 2010.

[37] J. D. Hunter, "Matplotlib: A 2D Graphics Environment," *Computing in Science & Engineering*, vol. 9, no. 3, 2007.

[38] P. Virtanen, R. Gommers, T. E. Oliphant, M. Haberland, T. Reddy, D. Cournapeau, E. Burovski, P. Peterson, W. Weckesser, J. Bright, S. J. van der Walt, M. Brett, J. Wilson, K. J. Millman, N. Mayorov, A. R. J. Nelson, E. Jones, R. Kern, E. Larson, C. J. Carey, Polat, Y. Feng, E. W. Moore, J. VanderPlas, D. Laxalde, J. Perktold, R. Cimrman, I. Henriksen, E. A. Quintero, C. R. Harris, A. M. Archibald, A. H. Ribeiro, F. Pedregosa, and P. van Mulbregt, "SciPy 1.0: fundamental algorithms for scientific computing in Python," *Nature Methods*, vol. 17, no. 3, 3 2020.

[39] "(PDF) Estimating the source of the negative potential that occurs before rapid eye movement during REM sleep: Analysis of recordings using a high-density electroencephalography (EEG)." [Online]. Available: https://www.researchgate.net/publication/351768758_Estimating_the_source_of_the_negative_potential_that_occurs_before_rapid_eye_movement_during_REM_sleep_Analysis_of_recordings_using_a_high-density_electroencephalography_EEG

[40] J. F. T. A. M. M. Andres Soler, Ole Drange, "Automatic Onset Detection of Rapid Eye Movements in REM Sleep EEG Data," 2021.

[41] "AASM Scoring Manual - American Academy of Sleep Medicine." [Online]. Available: https://aasm.org/clinical-resources/scoring-manual/

[42] "5. EVALUATION OF INVERSE METHODS AND HEAD MODELS FOR EEG SOURCE LOCALIZATION USING A HUMAN SKULL PHANTOM," Tech. Rep.

[43] J. C. F. De Winter, "Using the Student's t-test with extremely small sample sizes," *Practical Assessment, Research, and Evaluation Practical Assessment*, vol. 18, p. 10, 2013.

[44] M. R. Delgado, "Reward-Related Responses in the Human Striatum."

[45] A. L. Lalive, A. D. Lien, T. K. Roseberry, C. H. Donahue, and A. C. Kreitzer, "Motor thalamus supports striatum-driven reinforcement," *eLife*, vol. 7, 10 2018.

[46] R. Elliott, R. J. Dolan, and C. D. Frith, "Dissociable functions in the medial and lateral orbitofrontal cortex: Evidence from human neuroimaging studies," *Cerebral Cortex*, vol. 10, no. 3, pp. 308–317, 3 2000. [Online]. Available: https://academic.oup.com/cercor/article/10/3/308/449600

[47] J. Bigbee, "Postcentral Gyrus," in *Encyclopedia of Clinical Neuropsychology*. Springer New York, 2011, pp. 1972–1972. [Online]. Available: https://link.springer.com/referenceworkentry/10.1007/978-0-387-79948-3_353

[48] E. T. Rolls and F. Grabenhorst, "The orbitofrontal cortex and beyond: From affect to decision-making," pp. 216–244, 11 2008.

Appendix

A REM sleep stage finder

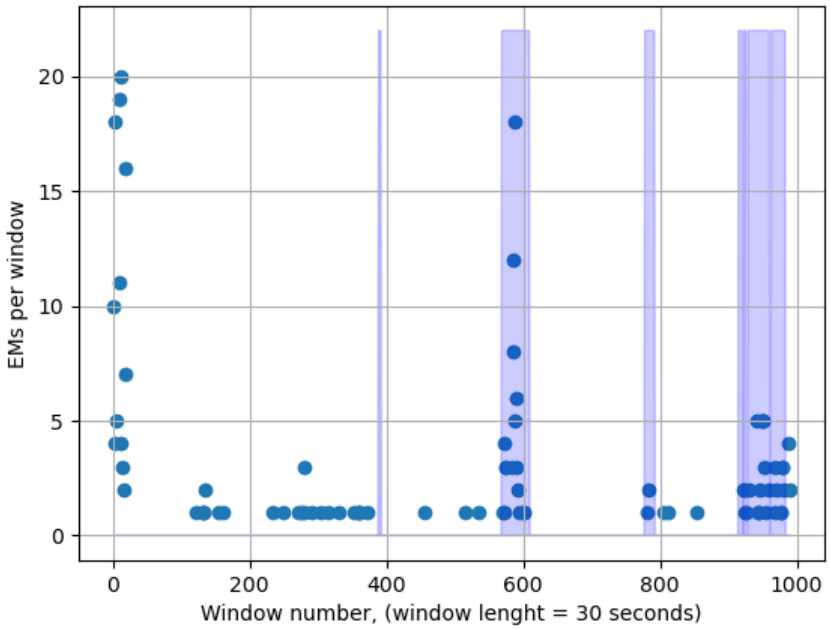


Figure 26: EMs found by algorithm in window comapired to sleep expert rated REM sleep stage for subject s129

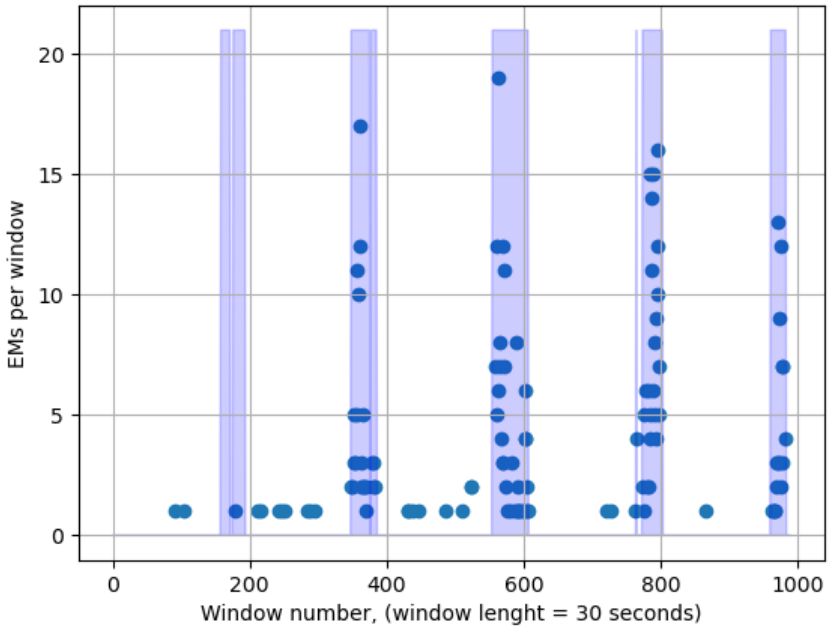


Figure 27: EMs found by algorithm in window comapired to sleep expert rated REM sleep stage for subject s240

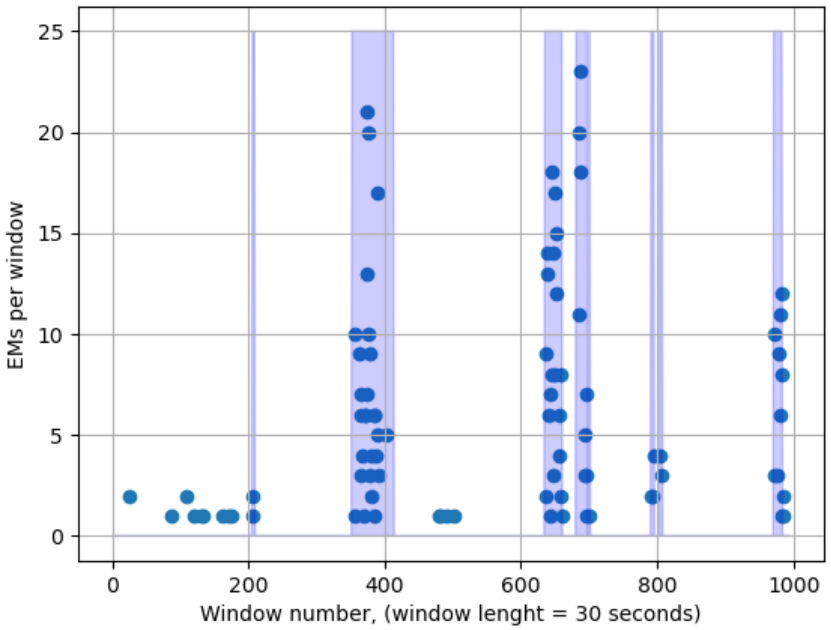


Figure 28: EMs found by algorithm in window comapired to sleep expert rated REM sleep stage for subject s241

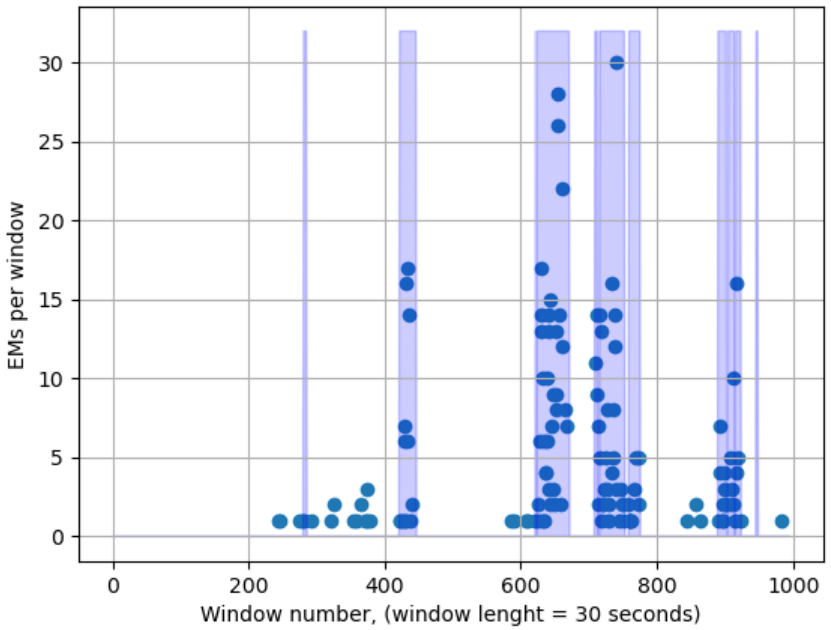


Figure 29: EMs found by algorithm in window comapired to sleep expert rated REM sleep stage for subject s242

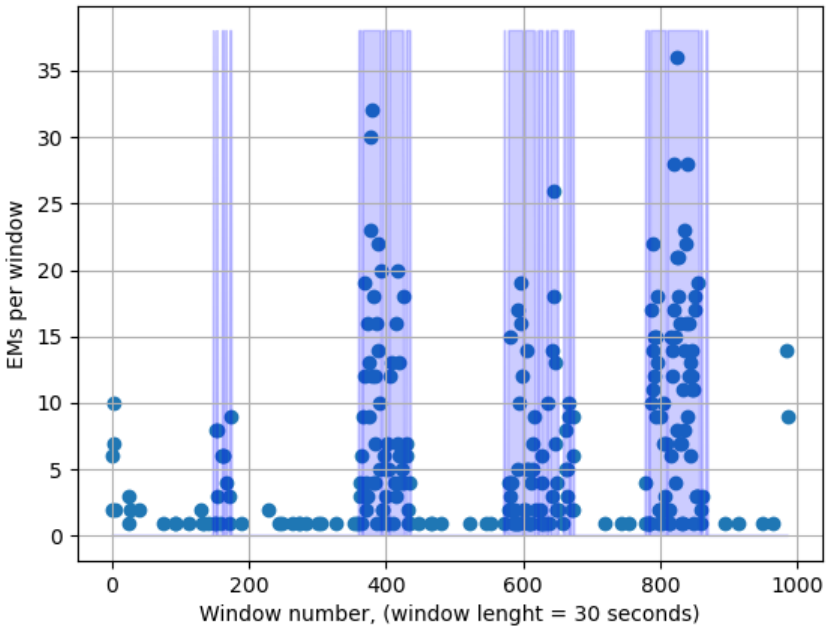


Figure 30: EMs found by algorithm in window comapired to sleep expert rated REM sleep stage for subject s247

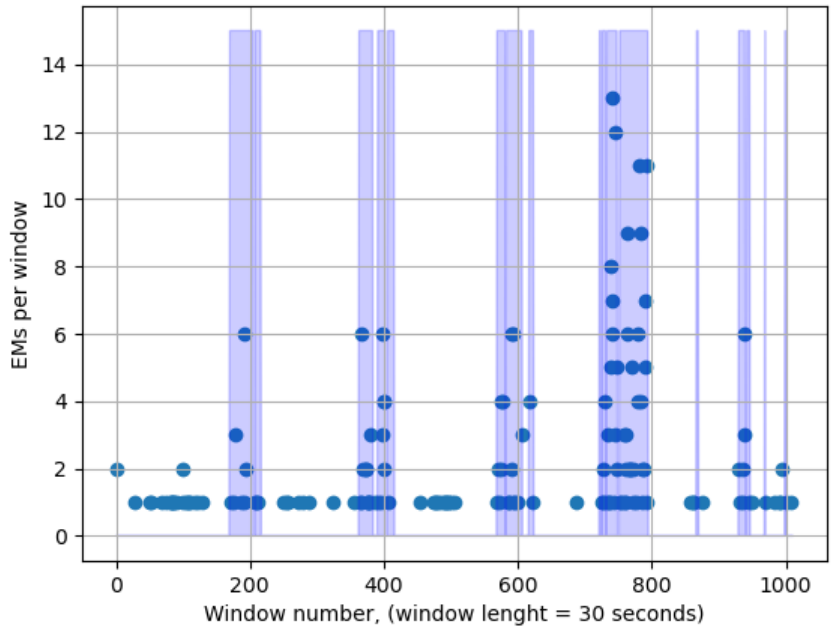


Figure 31: EMs found by algorithm in window comapired to sleep expert rated REM sleep stage for subject s248

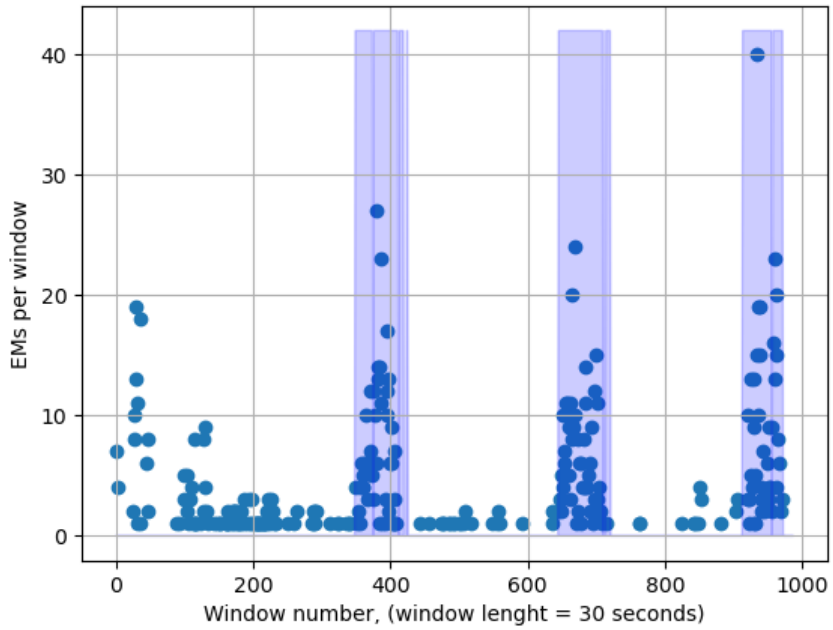
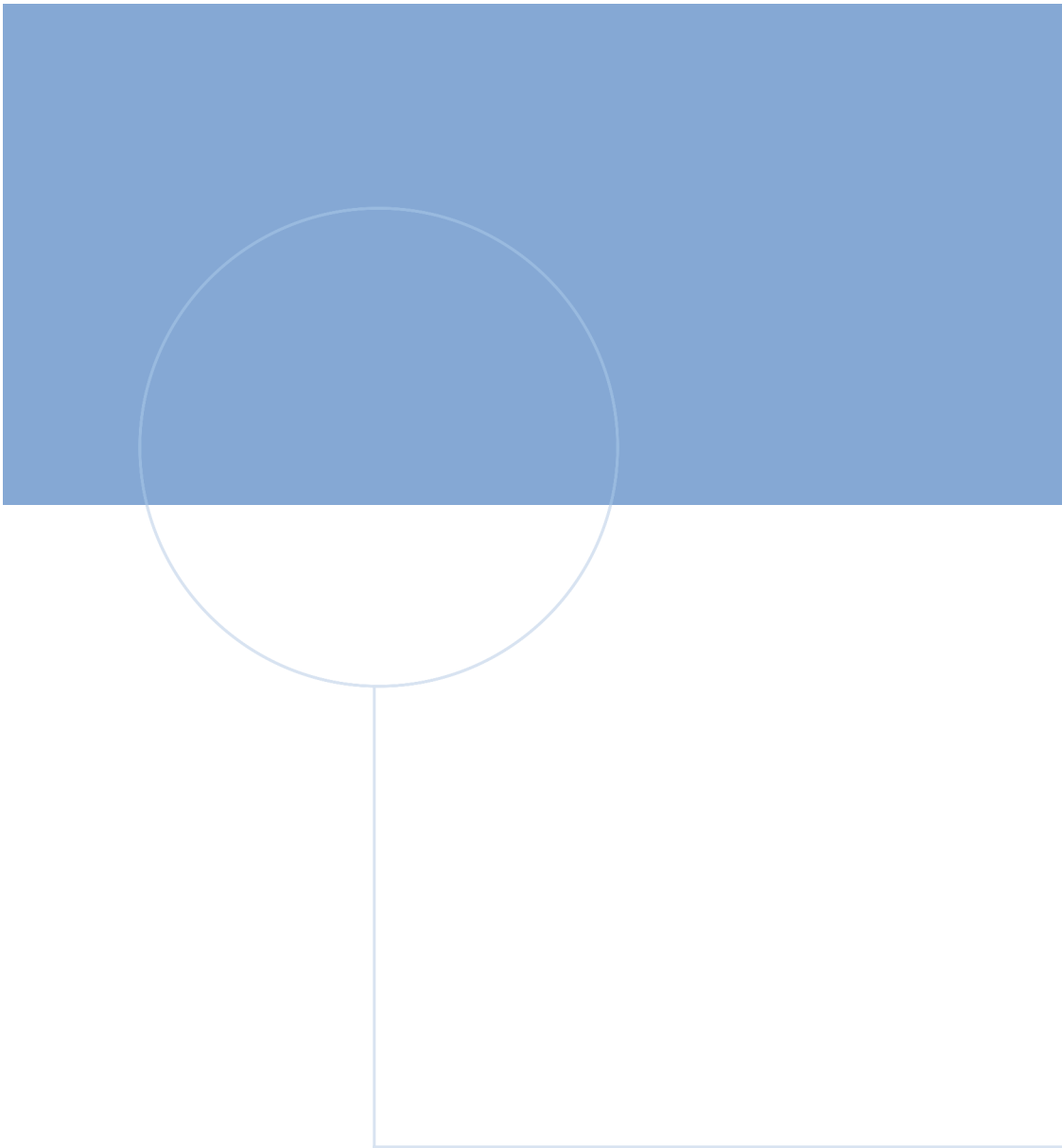


Figure 32: EMs found by algorithm in window comapired to sleep expert rated REM sleep stage for subject s300



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