Towards high-performance differentiation between Narcolepsy and Idiopathic Hypersomnia in 10 minute EEG recordings using a Novel Machine Learning Approach

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Abstract – While time and cost intensive tests are the current standard for diagnosing and classifying sleep disorders, we present results of using ten minute electroencephalographic recordings to differentiate between narcolepsy and idiopathic hypersomnia. Using a novel and fast machine learning approach, we reach an accuracy of almost 75 percent and moreover we show that there are systematic differences in the delta and beta-1 frequencies. For personalized treatments, it is important to differentiate between sleep disorders as they not only have side effects, but are also not equally effective for each respective sleep disorder.

Keywords – Narcolepsy, Idiopathic Hypersomnia, Machine Learning, Random Forests, Electroencephalography, Spectral analysis

I. INTRODUCTION

Patients with sleep disorders present a significantly higher risk when driving, hence it is important to diagnose and treat hypersomnolences [1]. Central hypersomnolences are a group of diseases characterized by excessive daytime sleepiness, among which are narcolepsy and idiopathic hypersomnia [2]. Due to the difficulty of classifying different sleep disorders, clinical trials are rare [3]. Patients suffering from idiopathic hypersomnia often receive the same treatment as narcolepsy patients. The same medicines impact each hypersomnolence regarding sleepiness, but side effects are stronger for idiopathic hypersomnia patients [4, 5]. Furthermore, treatments are often only effective in the short term for idiopathic hypersomnia patients [3] and the issue of awakenings cannot be resolved with these treatments [6].

Polysomnography (PSG) and Multiple Sleep Latency Test (MSLT) are the main tests when diagnosing hypersomnolences. In the MSLT, different sensors measure data such as electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), electrocardiogram (ECG) to extract information about sleepiness and the presence of abnormal sleep onset rapid eye movement (REM) episodes [7]. These tests produce a huge amount of data. To interpret this data, machine learning can be an effective approach. Machine learning techniques can make an impact in healthcare [8]. At present, no studies have used only EEG data to differentiate between narcolepsy and idiopathic hypersomnia.

<table>
<thead>
<tr>
<th>Table 1: Standard EEG bandwidths [9-11]</th>
</tr>
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<tbody>
<tr>
<td>Frequency Band</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>Delta</td>
</tr>
<tr>
<td>Theta</td>
</tr>
<tr>
<td>Alpha</td>
</tr>
<tr>
<td>Beta</td>
</tr>
<tr>
<td>Gamma</td>
</tr>
</tbody>
</table>

If EEG is applied to narcolepsy and idiopathic hypersomnia patients, differences within the delta band power (amplitude) can be observed [12].

Using the novel method by Rieg et al. [9] we contribute to an easier differentiation and therefore a more personalized treatment of each disorder. The four most important contributions from this work are:

1. It is shown that it is possible to differentiate between the disorders using EEG data.
2. Only 10 minute snippets of EEG recordings are required for the differentiation. Long and cost intensive tests like the MSLT and PSG can be replaced with 10 minute EEG recordings.
3. Furthermore, the meaning of the delta area for the classification is proven. In particular, the frequency bands from 0.5 to 3 Hz are relevant for the diagnosis of idiopathic hypersomnia.
4. Narcolepsy patients show a higher spectrum in the beta-1 area.

The paper is organized as follows: Next we present an overview of the research background on narcolepsy, idiopathic hypersomnia, MSLT and PSG and related work. After that we detail the research methodology, including information about the dataset, EEG noise removal and the machine learning method used, the Random Forest. After that we present the machine learning results concerning the accuracy, variable importance and most important variables. Afterwards we discuss the results. Finally we conclude with limitations and ideas for future research.
II. RESEARCH BACKGROUND

A. Sleep disorders

Narcolepsy patients suffer from periods of irresistible sleep of brief duration [13]. There are two types of narcolepsy: with and without cataplexy. Narcolepsy with cataplexy is also called Type 1 narcolepsy and can be diagnosed by HLA (human leukocyte antigen) DQB1*0602 positivity and with low hypocretin-1 [14]. While it is easy to diagnose narcolepsy with cataplexy, diagnosing narcolepsy without cataplexy (Type 2 narcolepsy) is often difficult as there are nonspecific symptoms and current diagnostic tests are limited [15]. Another sleep disorder is idiopathic hypersomnia. There are no clinical features to diagnose idiopathic hypersomnia, so it can only be diagnosed by excluding other sleep disorders [12]. Patients with idiopathic hypersomnia tend to have longer mean sleep latencies as the sleep periods are not as irresistible as in narcolepsy and they have a normal sleep efficacy higher than narcolepsy patients [4]. Idiopathic hypersomnia is often over-diagnosed. As there are no criteria like cataplexy in this disorder, many sleep disorders are frequently mistaken and diagnosed as idiopathic hypersomnia when the patient is not examined on all possible clinical features of other sleep disorders [16]. Idiopathic hypersomnia had been divided into 2 forms before, but now it has been merged into one [6]. The International Classification of Sleep Disorders (ICSD) is a classification system for sleep disorders, published by the American Academy of Sleep Medicine (AASM). In 2014 a new version, ISCD-3, had been published which shows that classification is not easy and has been revised multiple times.

As an accurate diagnosis and classification of sleep disorders is challenging, not many clinical trials have been conducted to find personalized medicine for each of the two hypersomnias [3]. Both idiopathic hypersomnia and narcolepsy patients are mainly treated to reduce the daytime sleepiness. Treatments with modafinil, methylphenidate, and dextroamphetamine, are common. While these seem to work really well for narcolepsy, the results for idiopathic hypersomnia patients are often less than satisfactory [17]. The sleepiness can be reduced in both hypersomnolences, but side effects are stronger for hypersomnia patients [4-5] and they are often only effective in the short term [3]. Idiopathic hypersomnia patients are excessively sleepy during the day and have great difficulty being awakened from sleep, something that cannot be treated with the aforementioned medicines [6]. Therefore, differentiation is essential for diagnosing the sleep disorder and the appropriate treatment.

B. Polysomnography and Multiple Sleep Latency Test

The Multiple Sleep Latency Test (MSLT) is the standard measure for assessment and diagnosis of excessive daytime sleepiness. In this test many sensors record data like EEG, EOG, EMG, ECG. The test is split in 2-hour intervals which are repeated at least four times within a day. With the MSLT the speed of falling asleep can be measured [7]. The MSLT needs to be performed after an overnight Polysomnography (PSG). The PSG is a common method for the assessment of sleep disorders. The overnight measurement includes EEG, EOG, EMG, ECG, air flow, respiratory effort, and oxygen saturation [18]. Studies show that PSG results are different in a clinical environment versus at home [19]. Considering the time and cost of intensive tests and the biased results if tests are carried out in a clinical environment, a need for alternatives is evident.

C. Related Work

Looking at other results there is only one other work on differentiating narcolepsy and idiopathic hypersomnia by using EEG data and a machine learning method. The details of this work can be seen in table 2. When investigating this publication, it was found that EEG data from different trials had been used: data from the Stanford Narcolepsy Center was combined with a control group from the Wisconsin Sleep Cohort. The Stanford data was collected using a Sandman SD32+ amplifier and for recording the Wisconsin Sleep Cohort data, a 16-channel Grass-Telefactor Heritage digital sleep system Model 15 was used [20]. As different devices have been used for recording the data, there is a possibility that the algorithm could have detected differences in the data caused by the devices itself. This is why we do not consider the paper to be comparable.

### Table 2. Related Work

<table>
<thead>
<tr>
<th>Year</th>
<th>Reference</th>
<th>Data</th>
<th>Method</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018</td>
<td>Jiang et al. [21]</td>
<td>MSLT</td>
<td>Different machine-learning models</td>
<td>Accuracy 50 - 95%</td>
</tr>
</tbody>
</table>

III. METHODS

The design science approach [22] is used. The contribution is an algorithm based on the method of splitting EEG in 99 frequency bands according to [9].

A. Dataset

The dataset which is used in this paper was recorded as part of a huge observational study the aim of which was to identify patients with narcolepsy/ hypocretin deficiency with different samples. Therefore, different sleep studies were performed in university medical centers in the United States, Europe, China and Korea [23].

In this publication we only use the dataset which was recorded in Korea (patient-based Korean Hypersomnia Cohort, KHC). The dataset was recorded at St Vincent’s Hospital in Suwon in cooperation with Stanford University [24]. The self-identified ethnicity of all patients was Asian [14, 23, 24]. The EEG recording protocol is shown in [10, 23] and the full dataset can be downloaded from https://stanfordmedicine.app.box.com/s/r9e92yy9g0er77hn5re6j51aaggf509ly.

The dataset used consists of 3,168 recordings with a frequency of 200 Hz [24-25]. 1,584 of the recordings are from patients with narcolepsy, the others are of patients with idiopathic hypersomnia. The length of all recordings is about 10 minutes. Time of simulation was varied. The dataset
contains data from 6 EEG sensors, which are positioned by the 10-20 EEG system [26]. The 10-20 EEG procedure is described in [25]. Fig. 1 shows the position of the sensors in a 10-20 EEG system [24-25] and the position of the 6 electrodes used.

Figure 1. EEG sensor position [25] and used electrodes [26]

B. EEG noise removal

A big problem of EEG data is noise generated during data collection. Some examples of these noises are muscle activities, eye movement, blinking and heartbeat [27]. Another problem of EEG data is that the electrodes record mixed signals. Signals which are recorded by one electrode can also be seen on the recording of another electrode [28]. So it is necessary to clean the data up. In the past several methods were used for this. A commonly used method was the regression in the time or frequency domain. The aim of this method was to establish parameters characterizing the aspects and spread of the EEG data. However, by using regression it is not possible to filter out muscle movements because there is no reference for them [27]. Another alternative was to ask the proband to avoid blinking. Furthermore, the principal component analysis was used to filter the interfering signals [29].

Due to this, Bell and Sejnowski developed the Independent Component Analysis (ICA), which can solve that blind separation task [30]. This method is a linear decomposition approach, which can be used on EEG data to correct them. The ICA based on spiral filtering, and because of that there is no need for a clean reference channel. The ICA is able to decompose multiple-channel EEG data to spatially-fixed and temporally independent components in an effective way. It is a neuronal network algorithm, which is able to blindly separate mixtures (x), with independent sources (s) by using an infomax. There is a need that nonlinearity is given. By analyzing EEG data, the rows of the input Matrix (x) are the signals which were recorded by the EEG electrodes. The data in the output matrix u = Wx are time courses of activation by the units of the ICA and also the columns of the inverse matrix W⁻¹. The projection power of the specific electrode unit. The scalp topographies of the signal supply evidence of the biological source. Altogether the time component, because of activation, will not be orthogonal. The corrected EEG signals are corresponding to x’ = (W)ᵀu’, where the term u’ is the matrix of the excitation waves, and where the rows which represent artifacts are set to zero.

C. Machine Learning Method

This part of the paper explains the machine learning method used to distinguish between narcolepsy and idiopathic hypersomnia.

a) Spectral Analysis and Feature Extraction

The common division into the five frequency bands, alpha, beta, theta, delta and gamma, was not used in this work. Instead, the bands were divided into 99 frequency bands, in the range from 0.5 to 50 Hz. Each of these 99 frequency bands has a span of 0.5 Hz. This method was invented by Rieg et al. [9]. The hypothesis behind this is that the information content of finer frequency bands is higher. It is possible that there is a lot of information in a specific frequency band, which is not useful for the prediction of narcolepsy and idiopathic hypersomnia. So the relevant information density can be reduced. To get the best possible result the information density should be as high as possible [9].

After the EEG Signal is cleaned by the ICA, it has to be transformed into a frequency signal [31]. This goal is achieved by a spectral analysis. In the neurosciences the spectral analysis is often used. It has originated many new findings regarding the brain. The spectral analysis is done with a Fast Fourier Transform. In the traditional Fourier Transform the EEG signals are broken down into sinusoid oscillations which have a known wavelength [32]. After that each wavelength is checked for accordance with the EEG signal. The aid is a correlation analysis. The result of the Fourier transformation, called a power spectrum, is to allow the distribution of frequencies of the EEG signal to be estimated. By using the power spectrum it is possible to recognize EEG signal components. This shows the highest activity in the frequency bands. [9, 32, 33]

b) Classification

The machine learning method which is chosen for classification of narcolepsy and idiopathic hypersomnia is the Random Forest introduced by Breiman in 2001 [34, 35]. In R the Random Forest from the caret package was used for the classification [36]. The division was as described in the following: Training 75% (2,377 records) and test 25% (792 records). For each 10 replications were made. 100 trees were used (n=100), furthermore the variable importance, which is calculated by Random Forest, is displayed. The variable importance is based on the statistical significance of the variable and its influence on the Random Forest model. See [37] for explanation.

c) Validation

The method was supplemented by cross-validation for a reliable value. It was carried out with a repeated cv which was done 10 times. It is thus possible to see which subjects were classified correctly and which not, based on the trained model. To reach this aim, the cross-validation matrix of the model was built. The cross-validation classifies as follows:

(1) True positive: The subject has narcolepsy and the test has correctly indicated it; (2) False negative: The subject has narcolepsy but the model has falsely classified him as...
idiopathic hypersomnia; (3) False positive: The subject is an idiopathic hypersomnia patient but the model has classified him as a narcolepsy patient; (4) True negative: The patient is an idiopathic hypersomnia patient and has been classified as an idiopathic hypersomnia patient by the model. Information about the sturdiness of the model is provided by the cross validation. The following chapter shows the cross-validation matrix. In addition, the accuracy of the model is calculated [9]. This is followed by the variable importance for all frequency bands and a closer look at the five most important frequency bands.

IV. RESULTS

Random Forest was trained with 2,377 records and tested with 792 records. The respective EEG power band spans were 0.5 Hz. The 10-CV was repeated 10 times on the training set. The resulting confusion matrix is shown in table 3. The accuracy was 74.87% while the prevalence of narcolepsy was 50% (table 4).

<table>
<thead>
<tr>
<th>Reference</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Narcolepsy</td>
<td>302</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>94</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Predicted</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Narcolepsy</td>
<td>105</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>291</td>
</tr>
</tbody>
</table>

TABLE 3. CONFUSION MATRIX

The frequency bands are assigned to the standard EEG bandwidths. The frequency bands with the most prediction power are highlighted in figure 3.

<table>
<thead>
<tr>
<th>Performance indicator</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy</td>
<td>74.87%</td>
</tr>
<tr>
<td>True positive rate</td>
<td>76.26%</td>
</tr>
<tr>
<td>True negative rate</td>
<td>73.48%</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>74.20%</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>75.58%</td>
</tr>
<tr>
<td>Balanced accuracy</td>
<td>74.87%</td>
</tr>
<tr>
<td>Kappa</td>
<td>49.75%</td>
</tr>
</tbody>
</table>

TABLE 4. PERFORMANCE

Fig. 2 shows the variable importance of all bands.

The most important frequency bands  are also shown in figure 4. A difference to figure 3 is that the numbers are not scaled to 100. Furthermore, in figure 4 the importance of the frequency bands is shown for narcolepsy and idiopathic hypersomnia.

Figure 2. Variable importance

Figure 3. Most important frequency bands

Figure 4. Most important frequency bands

Table 5 shows the important frequency bands (fb) detecting narcolepsy (Narco) or idiopathic hypersomnia (IHyp).

**TABLE 5. TOP 5 VARIABLE IMPORTANCE**

<table>
<thead>
<tr>
<th>fb (Hz)</th>
<th>Narco</th>
<th>IHyp</th>
<th>Cohen's d</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5-1</td>
<td>13.73</td>
<td>9.60</td>
<td>-0.0938</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1.5-2</td>
<td>14.47</td>
<td>12.57</td>
<td>-0.2584</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1-1.5</td>
<td>25.53</td>
<td>20.58</td>
<td>-0.2580</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2-2.5</td>
<td>10.93</td>
<td>7.43</td>
<td>-0.1160</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>14.5-15</td>
<td>8.01</td>
<td>9.64</td>
<td>-0.1587</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

V. DISCUSSION

While the differentiation of narcolepsy and idiopathic hypersomnia is achieved with an accuracy of 74.84 %, in figures 2 and 3 it is shown that most of the most important variables are the frequency bands between 0.5 and 3.5 Hz.

In the standard EEG bandwidths this is called the delta area. The delta area includes five frequency bands with the bandwidth of 0.5 Hz. All of them are in the top 10 of the most important frequency bands. Furthermore, four of these five frequency bands are in the top 5 of the most important bands, which are shown in figure 4 and table 5. As shown in figure 4 the importance of the first band which is not in the delta area, 14.5 to 15 Hz, has only half of the importance of the most important frequency band in the delta area. Pizza et al. have shown that delta power is higher in idiopathic hypersomnia than in narcolepsy [12]. This matches with the point that patients with idiopathic hypersomnia have longer sleep latencies [4]. This underlines also why idiopathic hypersomnia patients have problems awakening [6].

The variable importance of the frequency bands is not equal for narcolepsy and idiopathic hypersomnia. This is shown in figure 4 and table 5. In the frequency bands of the delta area the patients with narcolepsy have a higher impact on the importance of the frequency bands than the patients with idiopathic hypersomnia. On the other hand, the frequency band of 14.5 to 15 Hz, which is in the beta-1 area, is more important for the detection of idiopathic hypersomnia. This could also cohere with the fact that patients with idiopathic hypersomnia have longer sleep times [4]. As shown in table 5, all these differences are significant (p<0.001) while the effect sizes are small (Cohen’s d <0.3).

In contrast to Jiang et al. [21], the differentiation is stable. Furthermore, the recording time of 10 minutes is better than an hour-long MSLT following an overnight PSG.

VI. CONCLUSION

In this work the way towards differentiating between narcolepsy and idiopathic hypersomnia with EEG data is shown. In this context the delta frequency bands are important for the differentiation. Because of the use of more frequency bands than the five standard EEG areas it was possible to show the importance of the delta area for differentiation. The finer classification allows a detailed discussion of the single EEG areas. As shown in figure 4, while the lower frequencies from 0.5-2.5 Hz are increased in narcolepsy, while the band from 14-14.5 Hz is decreased (p<0.001).

The differentiation of narcolepsy and idiopathic hypersomnia is a step towards personalized medicine. For now, patients with idiopathic hypersomnia receive the same drugs as patients with narcolepsy [39]. The current differentiation of narcolepsy and idiopathic hypersomnia only works with tests like MSLT or PSG, which includes more data than just EEG. A differentiation which just uses a 10 minute EEG is not as cost-intensive as the other methods. Furthermore, the length of the used recordings, 10 minutes, is much shorter than an overnight PSG or MSLT.

A. Limitations

A limitation of our work is the labelling of the participants. Idiopathic hypersomnia in particular is difficult to diagnose, because it is often just identified by an exclusion diagnosis [12]. Furthermore, medication and individual personality [40, 41] influence EEG and potentially bias the data. A practical limitation is the absence of external validation. For that the system has to be tested in a daily hospital routine. A future limitation is the lack of acceptance of the system among doctors. They first have to be convinced of it.

From a methodological point of view we have intensively evaluated other traditional machine learning approaches such as clustering [42] and also most modern convolutional neural networks, which are outstanding in other domains such as image recognition [43-45], but here we achieved the best results just with our novel method proposed in [9]. However, the method of choice always limits scientific understanding.

B. Future work

In future work we will report common method bias evaluations [46, 47], especially based on larger datasets from various social groups. To improve accuracy we will also triangulate EEG sensor data with other physiological sensor data (i.e., electrocardiogram [48, 49], electrodermal activity [50, 51], eye fixation [52-54], eye pupil diameter [55-58]) to substantially improve the accuracy. Furthermore, we will experimentally evaluate whether our novel approach is also robust under various conditions of a user's cognitive workload [59-62], concentration [63], and mindfulness [64, 65]. In addition, we will report results on successfully applying our novel procedure to other diseases such as epilepsy [66], sleep disorder [67], and schizophrenia [68, 69].

In terms of implementing the approach in real clinical environments, we will conduct an implementation study to test acceptance [70-72] and trust [73] by physicians and patients and to establish whether the automated approach improves coordination [74-76] between physicians more efficiently.

ACKNOWLEDGMENT

We thank the reviewers, who provided very helpful feedback on the refinement of the paper. This work is partly funded by the German Federal Ministry of Education and Research (13FH4E03IA, 13FH176PX8).

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