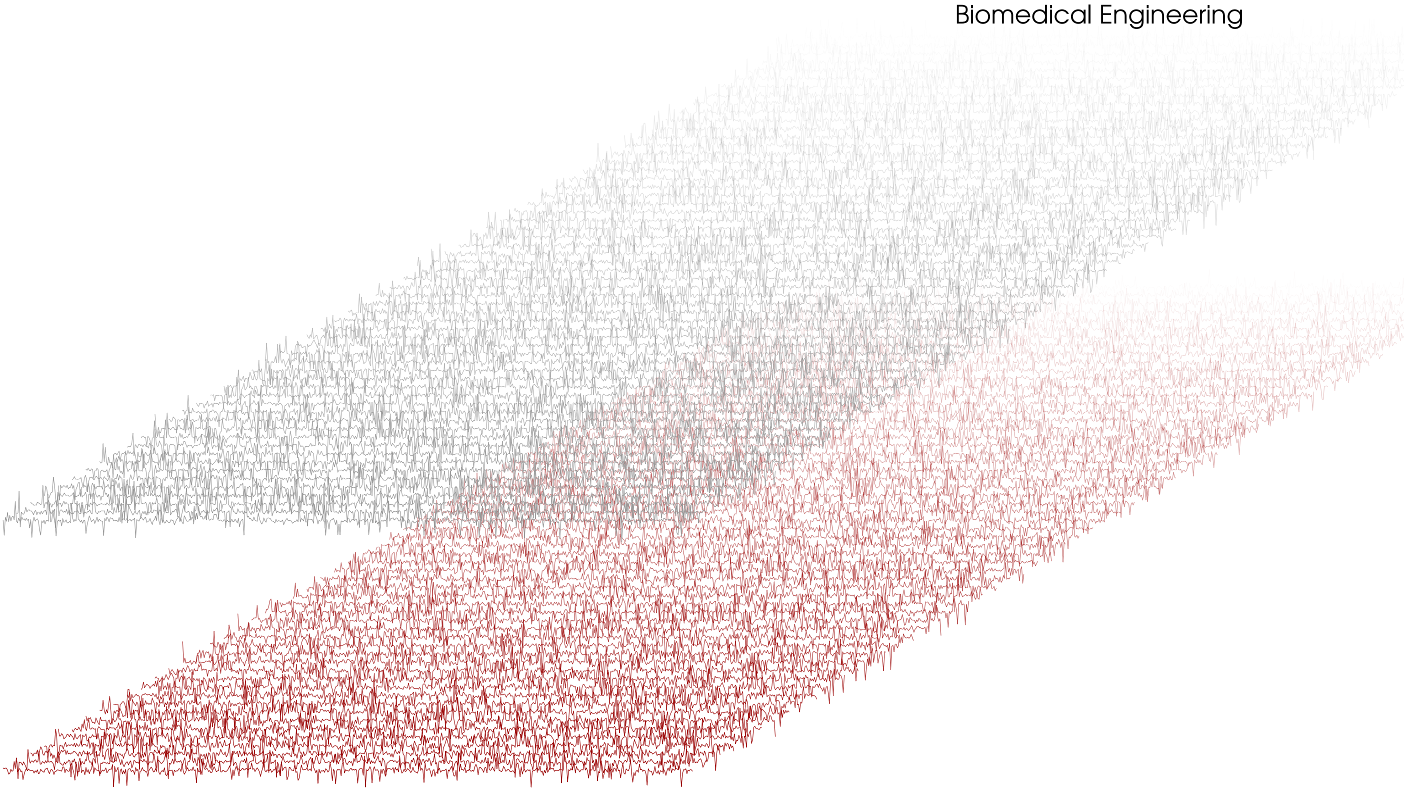
M.Sc. Thesis (2018)
Biomedical Engineering



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Machine learning and early biomarkers in stroke treatment

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Project overview

The following document provides an overview of the thesis titled "Machine learning and early biomarkers in stroke treatment". For in-depth information on the studies presented in this overview, the author refers to the thesis itself.

In the present overview a combined abstract for the project is initially given. The project was structured as three studies, and following the overall abstract, three study-specific abstracts are provided along with a key figure from each study.

The code repository developed for doing the deep learning studies is available at `https://github.com/rasthh/stroke-deep-learning`. Within the repository a description of the code used (documentation in README.MD) is available, along with examples of running (parts of) the code in Jupyter notebooks. The scripts for running the analyses on Sherlock is given, as well as the resources needed to replicate the study (e.g. the script that generated the cross-validations splits, i.e. IDs used for training and evaluation, as well as the specific IDs used).

Abstract

Introduction Stroke is one of the most severe cardiovascular diseases, and stroke is affecting a large portion of the population. Improvement of the diagnosis and treatment of stroke is of great importance for public health, especially in a steadily older population. Since stroke is the second largest cause of death worldwide, stroke has been likened to an actual epidemic In addition to being the source of significant morbidity and mortality, stroke has considerable socio-economic consequences. Biological pre-stroke markers of stroke risk and post-stroke markers of disease outcome are of significant interest. Such markers can be used to e.g. guide preventative stroke treatment and reduce stroke mortality. Studies of sleep in stroke patients have shown promise in being able to indicate both stroke risk and mortality risk from polysomnography studies (PSGs). The aim of the currently presented research is to investigate early biological markers of stroke risk and stroke mortality in PSG. Three studies are presented: (1) a study on the development of a method for post-hoc interpretability of deep learning algorithms applied on electroencephalography (EEG) data from PSGs, (2) an investigation of the prediction of 2 year stroke risk using deep learning on EEG, and (3) a study of mortality in stroke patients based on their PSG.

Methods In (1) the developed method, high-relevance epoch clustering (HiREC), is applied to a simulated problem and real sleep staging problem, and together the two experiments form a proof-of-concept for the proposed method. In (2), a deep learning network is developed and trained for the prediction of subjects with incident stroke within 2 years in the Sleep Heart Health Study against a matched control group. Additionally, the method developed in (1) is applied to the model trained in (2). Lastly, in (3) the PSG from subacute stroke patients is investigated using quantitative EEG analysis (spectral analysis) and compared to mortality data using a Cox regression.

Results Application of HiREC in (1) to the simulated problem correctly identified the simulated class markers. For the sleep stage scoring problem, the method e.g. identified epochs of eye movements to the rapid eye movement (REM) class and epochs with chin muscle activity to the non-REM 2 class. The developed network in (2) achieved an accuracy of 57 % in prediction stroke within two years, and application of HiREC to the model e.g. identified stroke-like epochs as epochs of motion artefact preceded by more regular waveforms and it identified non-stroke-like epochs as epochs with well-defined complexes. Spectral analysis of non-survivors in (3) showed that they especially displayed lower relative energies in higher frequency bands during non-REM 1 and 2 and REM.

Analysis The correct identification of simulated classes, and correct identification of defining characteristics for the investigated sleep stages, in (1) provide the basis that HiREC can, given a well-trained network, provide interpretable class representation, which is further corroborated by its successful application in (2). The neural network developed for stroke prediction (2) provides good indications that early biomarkers of stroke can be determined from the PSG. In (3) a score of lower relative energies was significantly associated with increased mortality-risk with a hazard ratio of 2.4, which was still significant when correcting for other known risk factors, thus indicating a significant effect of the spectral findings for stroke mortality.

Discussion The application of HiREC (1) to a deep learning model is a step towards improved adoption of high-performance, complex deep learning models to be adopted in applications, such as medicine, where their lack of interpretability was a barrier. HiREC can be utilized both as a means of improving existing models, to explain single model predictions in a broader context and as a guide for further studies of biomarkers. The network for stroke prediction (2) in its current form has an accuracy that needs to be optimized prior to utilization within e.g. stroke screening for preventative treatment. Numerous avenues of such optimizations are readily available, such as more complex architectures, larger datasets, and transfer learning; there is much promise in the prediction of incident stroke using EEG data and deep learning. The study of stroke mortality shows how relatively simple spectral analysis in relation to sleep staging can be used in assessing stroke mortality-risk. The currently presented spectral analysis under-utilizes the information present within the long PSG records. Additionally, certain features reported to be of interest in EEG (e.g brain symmetry indices) should also be investigated. The methods applied in (1) was directly applied in (2), and it is worthwhile noting how the approach in these can be used in identifying new biomarkers of interest to be studied in a manner similar to the approach in (3). Similarly, mortality-biomarkers could be investigated using the same methods as applied in (1-2).

Conclusion Early biological markers of both stroke risk and stroke mortality are evident in the PSG. A method for the post-hoc interpretation of deep learning models has been presented and its utility in the analysis has been demonstrated on both simulated data, a sleep stage scoring problem, and in analysing a stroke prediction network. Additionally, a network capable of predicting incident stroke, indicating the presence of stroke risk biomarkers in PSG, was presented. Lastly, a score of lower relative energies in higher frequency bands was presented. Evidence was presented for the prognostic values of such a quantification in relation to sleep stages.

Interpretable end-to-end deep learning for EEG-based predictions

Abstract

Introduction: Deep learning models are becoming increasingly pervasive due to their capability for high performance and solving complex problems. The models, however, are difficult to interpret, which is a barrier to adoption of deep learning algorithms to e.g. medical applications.

Background: Efforts into developing methods for the posh-hoc interpretation of deep learning models is increasing, but the methods are mostly based in image recognition, and the methods accordingly needs adaptation if they are to be applied for time-series data. Additionally, the methods focus on either explaining predictions of a model based on data (data-driven) *or* determining how a model internally represents concepts (model-driven) seperated from actual input data.

Aim: The current study presents a method, high-relevance epoch clustering, for post-hoc deep learning model interpretation. The method builds upon existing methods (Taylor decomposition of the model function) in arriving at a method suited for interpreting deep learning models for time-series data such as electroencephalography data. Furthermore, the model enables a data-driven explanation of how a deep learning model internally presents classes by aggregating prediction explanations.

Methods: The method identifies parts of the data (epochs) that are of high relevance to predictions. A spectral description of the high-relevance epochs enables a clustering. Clusters of uniform high relevance for specific classes form the basis for interpreting model representation of classes. The method is applied to a model trained to discern between two simulated and easily interpretable classes to illustrate the utility of the method. Following this, the method is applied to a simplified sleep stage scoring problem to illustrate the methods applicability to real data (see Figure 1).

Results and conclusion: The method was applied to the simulated and real data. The methods applicability to the problems illustrates the method's successfulness in interpreting complex deep learning models.

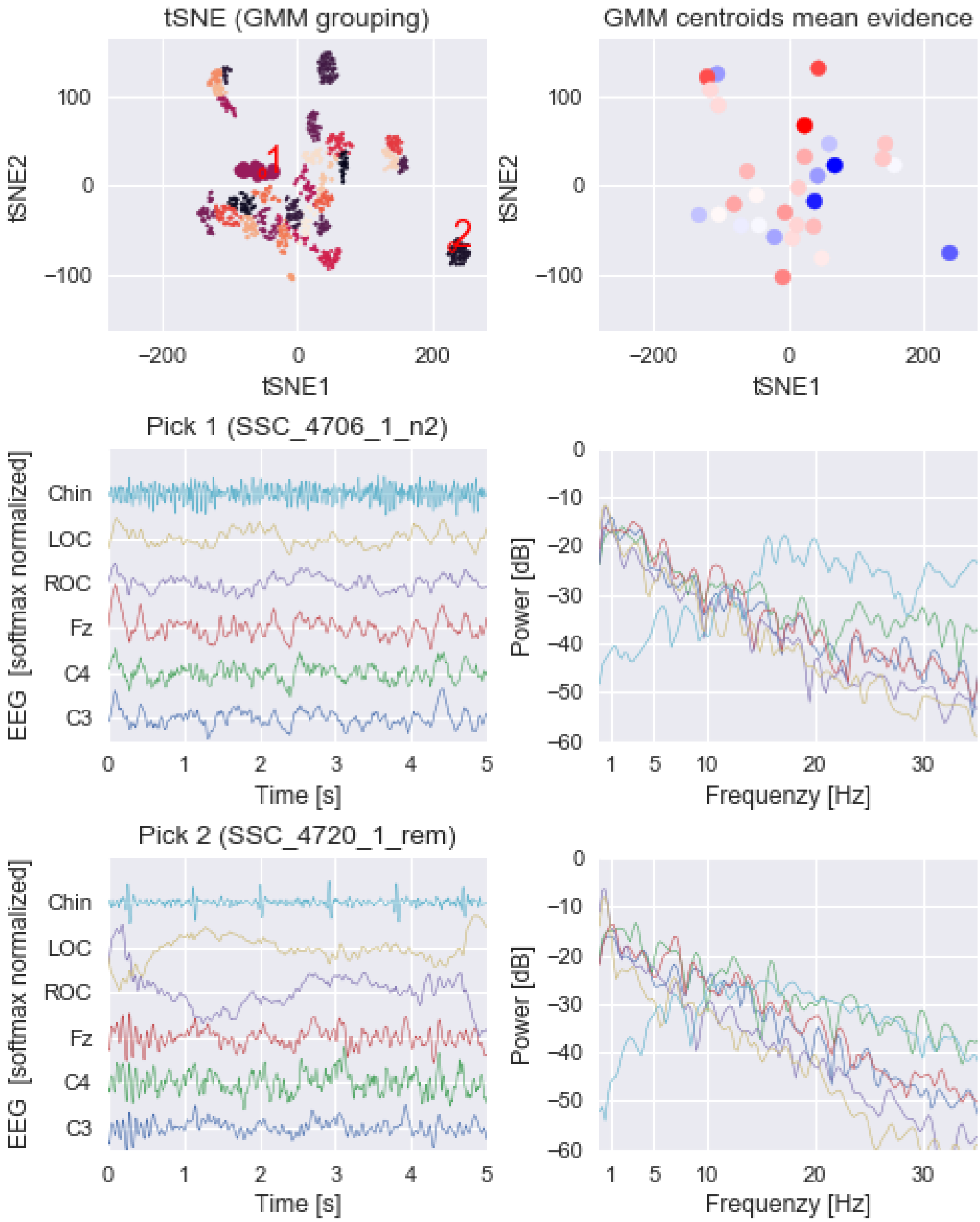

Figure 1: Visualization of high-evidence epochs of REM and N2 in spectral tSNE representation and with time-series and spectra for epochs within high-evidence clusters. Pick 1 displays chin EMG activity and N2-characteristic waveforms, whereas pick 2 shows clear eye movements in EOGs. These findings correspond to expectations of the stages and with the mean evidence for the clusters the epochs reside in.

Prediction of incident stroke using deep learning on 2-channel EEG

Abstract

Introduction: Stroke is one of the most severe cardiovascular disease affecting a large portion of population, causing significant morbidity and mortality, and stroke has considerable socio-economic consequences. Therefore, preventative treatment of stroke is of interest, which requires methods for assessing stroke risk. Cohorts of sleep studies are available, such as the Sleep Heart Health Study (SHHS), with incident stroke, enabling investigation of early indicators of stroke in the polysomnogram (PSG). PSG can be used to identify post-stroke stroke outcome and mortality-risk. The aim of the present study is to develop a deep learning model which can classify subjects that have a mortal stroke within 2 years based on EEG data. Additionally, post-hoc interpretation of the model will be applied in order to investigate if early biomarkers of stroke can be extracted from the model predictions for further studies.

Methods: Subjects from the SHHS that had a stroke within 2 years ($n = 76$) were matched against controls ($n = 76$) with no stroke in the follow-up based on available risk factors. A combination of a convolutional and a recurrent neural network was trained to classify each subject based on 2 EEG channels. For interpreting the model, high-relevance epoch clustering was applied to the trained model.

Results: A cross-validated accuracy of 57 % (sensitivity 57.5 % and specificity 56.2 %) was achieved. The significance of the accuracy being above chance was tested using a bootstrapping procedure, and the lower confidence limit was found to be above 50 %. Application of the post-hoc interpretation indicated that the non-stroke class was partially defined by epochs of highly regular sleep, whereas the stroke class was partially defined by epochs with arousals and artefacts (see Figure 2).

Conclusion: The developed model could predict stroke occurring within 2 years in the SHHS based on 2 EEG channels. The performance was, on average, not highly accurate. Various discussed avenues of optimization can likely provide a model that performs well enough to identify patients at risk of stroke, and thus identify targets of preventative treatment. The interpretation method provided insights into the class representations of the model that provide a basis for model improvement, but also prospective direction of further studies of the identified prospective biomarkers.

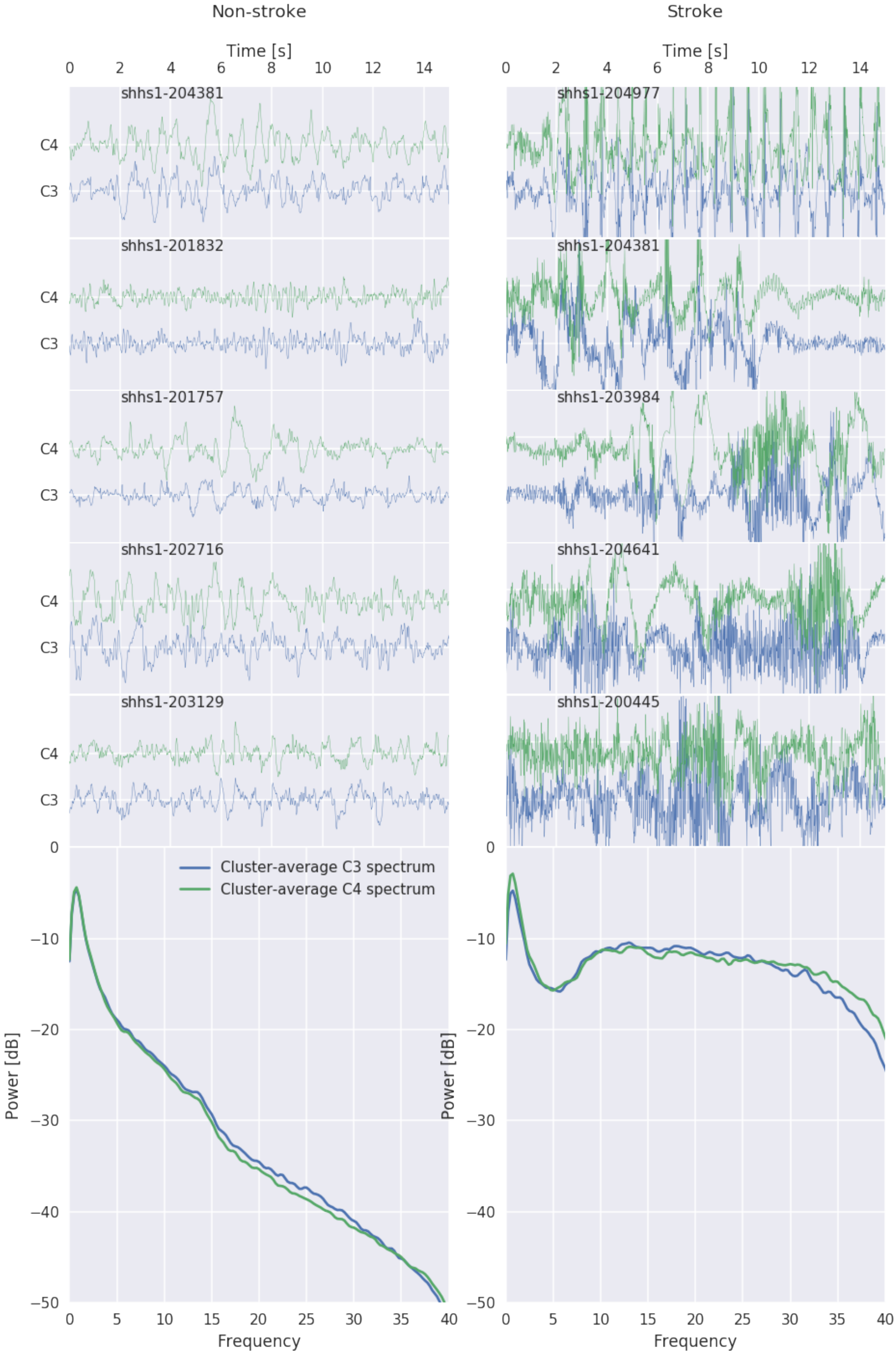

Figure 2: High-evidence clusters of non-stroke and stroke in prediction visualized by samples from cluster and cluster averaged spectra. *Left column*: non-stroke cluster, with time-series samples of important epochs in rows 1–5, and the cluster averaged spectra for each channel on the bottom. *Right column*: same plots as for the non-stroke cluster, but with samples from stroke cluster. The visualization of the cluster samples further corroborates the case-study of epochs that indicates that stroke was associated with noisy, possibly arousal, epochs, and non-stroke was associated with regular, non-noisy, epochs of waveforms regular to normal sleep.

Guidance of acute stroke treatment using quantitative electroencephalography from sleep studies

Abstract

Introduction: Brain activity dysfunctions in stroke patients are evident in the electroencephalography (EEG), and continuous EEG monitoring can be used as a way of determining severity and prognosis in acute stroke patients, but also as a way of predicting secondary injury. A study of polysomnography in stroke patients has shown that information (such as quantifications of sleep-related breathing disorders) derived from the sleep studies is associated with increased mortality. However, the EEG content of the stroke PSGs was unexplored. Therefore, the aim of the study was to determine indicators of increased mortality-risk based on the quantitative EEG changes in subacute stroke.

Methods: EEG spectral analysis was performed for PSGs from 56 patients with acute stroke or transient ischemic attack (recorded at a median of 3 days after stroke onset). The relative energy in traditional frequency bands for different sleep stages frontally, centrally, and occipitally were compared to mortality data (based on a 19–37-month follow-up period). An indicator of stroke mortality was tested using a Cox proportional hazards regression on a score of "lower relative energies" (LRE).

Results: In comparing mortality ($n = 9$) to survival ($n = 47$), mortality was associated with a lower relative energy especially in the β- and γ-bands (15–20hz, and 20–40 Hz, respectively) during REM, N1, and N2 sleep. This was tested by a two-sided two-sample t-test assuming unequal variances corrected for multiple comparisons (across sleep stages, channels and frequency bands) by estimation of the false discovery rate. Lower relative energies were associated with a increased hazard rate of 2.39 based on a dichotomization of LRE (see Figure 3).

Conclusion: Spectral analysis of the EEG in stroke patients measured during sleep showed that decreased lower relative energies in higher frequency bands were associated with stroke mortality.

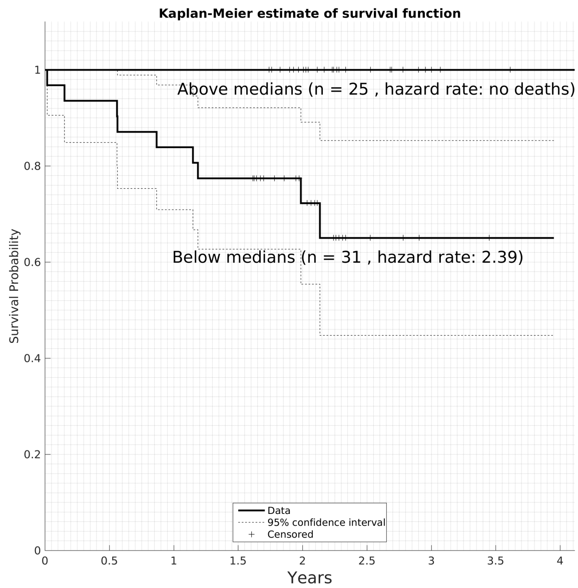

Figure 3: Kaplan-Meier survival curve for the two groups above and below median of the lower relative energy score. Lower relative energies are associated with an increased hazard ratio/lower survival probability.