Differentiating Ischemic Stroke Patients from Healthy Subjects Using a Large-Scale, Retrospective EEG Database and Machine Learning Methods

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Grant Support: National Science Foundation

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Running Title: EEG For Stroke Classification

Keywords: Electroencephalogram (EEG), Ischemic Stroke, Large Vessel Occlusion, Prehospital Stroke Scale, Feature Engineering, Machine Learning

ABSTRACT

Objectives: We set out to develop a machine learning model capable of distinguishing patients presenting with ischemic stroke from a healthy cohort of subjects. The model relies on a 3-minute resting electroencephalogram (EEG) recording from which features can be computed.

Materials and Methods: Using a large-scale, retrospective database of EEG recordings and matching clinical reports, we were able to construct a dataset of 1,385 healthy subjects and 374 stroke patients. With subjects often producing more than one recording per session, the final dataset consisted of 2,401 EEG recordings (63% healthy, 37% stroke).

Results: Using a proprietary set of features, our model yielded an AUC of 0.95 and sensitivity and specificity of 93% and 86%, respectively. Allowing for multiple recordings per subject in the training set boosted sensitivity by 7%, attributable to a more balanced dataset.

Conclusions: Our work demonstrates strong potential for the use of EEG in conjunction with machine learning methods to distinguish stroke patients from healthy subjects. Our approach provides a solution that is not only timely (3-minutes recording time or less) but also highly precise and accurate. Further validation aims to evaluate model performance in the prehospital setting.

1. INTRODUCTION

Background

Within the United States alone, a person dies of stroke every 3.6 minutes (1) and remains the leading cause of long-term disability worldwide. Stroke can be either ischemic or hemorrhagic. Ischemic stroke is due to the loss of blood supply to an area of the brain, whereas hemorrhagic stroke is the result of bleeding into the brain by the rupture of a blood vessel. A large majority of strokes are ischemic in nature and of all acute ischemic strokes (AIS), 46% are due to large vessel occlusion (LVO), which involves obstruction of large, proximal cerebral arteries (2). As stroke progresses without relief from treatment, there is significant time-dependent loss of brain tissue, affecting neurological recovery and functional outcome. Endovascular therapy (EVT) using mechanical thrombectomy, with or without intravenous thrombolysis (IVT) remains the leading treatment for LVO and has proven superior to standard medical care (3,4,5). However, not all hospitals in the United States are capable of providing EVT. A recent study found that only 37% of all stroke-centers were EVT capable and less than one-fifth of the US population had access to an EVT-capable hospital within 15 minutes (6). Thus, in the prehospital setting, early and accurate triage of patients eligible for such reperfusion therapies would be facilitated by improved methods for rapidly identifying patients with LVO appropriate for EVT.

To date, prehospital triage is conducted using available stroke scales. The American Heart Association/American Stroke Association commissioned a review committee to systematically review evidence for the accuracy of stroke prediction instruments. These assessments test between 3-7 items, all of which involve qualitative and subjective assessment on the part of EMS personnel. This subjectivity erodes the accuracy and precision of these assessments which have a reported sensitivity between 38-67%, with no existing clinical scale achieving >80%

sensitivity or specificity simultaneously (5). Thus, there remains a need for novel, objective technology that increases sensitivity of stroke diagnosis using the patient's own brain signals.

Electroencephalography (EEG) has long been known to have high sensitivity for immediate detection of brain ischemia (7,8,9). EEG has the potential to detect acute changes in brain function following onset of ischemia, even before cell death, providing tremendous benefit for early prehospital stroke diagnosis. Its application is commonly used for monitoring during carotid endarterectomy surgery. However, prehospital detection of stroke has largely been limited by EEG hardware accessibility and has yet been granted FDA-approval as a diagnostic tool, compared to radiological evaluations such as X-ray or CT. On the other hand, recent advances in EEG acquisition hardware, lead technology, and analysis software suggest a larger diagnostic role may be possible for patients with suspected acute stroke. In a recent study of 100 patients with suspected acute stroke in the emergency department (ED), EEG measures with clinical data (such as RACE scores, sex, age and time from last known well) increased sensitivity of stroke detection to 87.8% (9). Another study of 24 patients with suspected stroke in the emergency department found acceptable discriminative power for several frequency band power ratios between patients with and without an acute ischemic stroke with a large infarct volume (10). Similarly, preliminary results from the ELECTRA-STROKE (EEG Controlled Triage in the Ambulance for Acute Ischemic Stroke) study have established strong predictive power for theta/alpha ratio with an AUC of 0.83 (11). Despite the promising results, no large-scale study yet to be able to define a single EEG feature as a strong standalone diagnostic biomarker for stroke triage. Machine learning methods may provide a solution, offering a means of quantifying stroke likelihood given multiple EEG biomarkers.

Machine learning (ML) has recently gained momentum in the field of neurotechnology, especially in automated EEG analysis and clinical diagnostics. Its application has primarily been limited to predicting epileptic seizures or controlling neurostimulation parameters for stopping seizure activity (12). Recent work has attempted to expand this scope to stroke detection (8,9,11). However, due to the limited availability of clinical EEG databases, validation of these models becomes extremely difficult, impeding their adoption for use in a clinical setting. To this end, our work is built upon one of the largest public repositories of clinical EEG data available – Temple University Hospital EEG Data Corpus (TUH EEG; 13). This rich repository enabled us to train and validate our machine learning models using recordings from more than 1700 subjects, composed of both healthy and ischemic stroke patients.

2. METHODS

Data Description

The TUH EEG database represents one of the largest publicly accessible collections of electroencephalogram (EEG) recordings, hosting a substantial archive of 26,846 clinical EEG samples acquired from 14,987 patients at Temple University Hospital during the years 2002 to 2017. For our study, we meticulously selected patients devoid of neurological abnormalities and those with confirmed ischemic stroke. The identification of healthy subjects was achieved through a previously established TUH EEG segmentation, involving the manual review of clinical reports and EEG recordings (14). Furthermore, we applied a keyword-based approach to flag stroke cases, denoting an occlusion of the Middle Cerebral Artery (MCA), Internal Carotid Artery (ICA), Posterior Cerebral Artery (PCA) or Anterior Cerebral Artery (ACA). The matching clinical reports then underwent manual review to confirm ischemic stroke. The final dataset was made up of 1,385 healthy subjects from the initial curation and 374 stroke

patients from keyword search and manual confirmation. An additional 642 EEG samples were included (21% healthy, 79% stroke) due to the contribution of multiple EEG recordings by certain subjects. Together, a comprehensive dataset of 2,401 recordings (63% healthy, 37% stroke) was constructed and used for subsequent training and validation (Table 1).

In addition to collecting the clinical history from each report, demographic information was also extracted. For the cohort of stroke patients, mean age was 63.8 years with a standard deviation of 15.2 years (Table 2). Regarding the distribution by gender, males constituted 42% of the dataset, females 51%, with 7% missing gender description. Demographic information could not be obtained for the curated healthy cohort as clinical reports were not provided. However, the original authors of the TUH EEG segmentation, from which the healthy cohort was constructed, published demographic information from a subset of cases. The authors report a mean age of 46.6 years (standard deviation of 14.7 years), with a range of ages between 20 and 90. The distribution by gender was reportedly balanced between male and female cases, though the authors did not provide any quantitative details on the gender breakdown (14)

Preprocessing

All EEG recordings underwent resampling at a frequency of 100Hz, followed by the application of a bandpass filter within the 1 to 40 Hz range.

Feature Engineering

Quantitative EEG features were computed from a 3-minute window, where the start point defaulted to the first minute mark, reducing any potential bias from sensor calibration or excessive movement at the beginning of recording. Recordings lasting fewer than 2 minutes

were excluded from analysis, allowing for a minimum duration of 60 seconds to be used for feature engineering. The computed quantitative features encompassed recently published biomarkers, including spectral power ratios, relative powers by frequency band, sample entropy, and the brain symmetry index (5,6,7). A complete list of features and descriptions are provided under Table 3.

Frequency domain analysis remains a commonly applied technique for the evaluation of EEG. In patients suffering from ischemia, prior studies demonstrate a common pattern of slowing, characterized by an attenuation of faster frequencies (alpha and beta) and an increase in slower frequency (delta and theta) powers (15). To validate this biomarker for use in model development, we compared the mean powers of each frequency band (delta, theta, alpha, beta) between our healthy cohort and stroke subjects. The power spectrum was computed for each of the selected 19 sensors, arranged according to the International 10-20 system, and plotted on a topographical map for spatial analysis (Figure 1). Additionally, a Mann-Whitney U Test was performed to identify regions with the greatest degree of difference in power between the stroke and healthy groups (Figure 2). Within the slower frequencies, the difference in power was much more globally distributed, implying that transition to slower frequencies from brain ischemia is not always specific to one area. On the contrary, the differences in alpha and beta rhythms were more localized, with the greatest dissimilarity appearing within the occipital region, which could be attributed to a disruption of the posterior dominant rhythm.

Various time window (1-minute, 30-second, and 10-second) for feature extraction were experimented with, and the resulting esimates were compared against the 3-minute window benchmark. The intra-class correlation (ICC) was calculated to gauge the consistency of features derived from different time window sizes. This metric measures the statistical

similarity of intra-cluster estimates. In this case, it provides a strong metric for comparing similarity of feature estimates at different time windows against the 3-minute benchmark. Results are displayed in Figure 3.

As expected, reducing the time window dampened the reliability of feature estimates. The spectral ratios appeared most sensitive to reductions in window size. Upon further analysis, this was the result of one feature, specifically, the ratio between slower and faster frequency differences. Due to how this feature is derived, slight variations in the power spectrum can give rise to significant outliers. Therefore, any subtle change to the size of the time window can produce inconsistent estimates for this feature. As a result, the default 3-minute window was selected. In the future, reductions in the window size may be tested, but alterations to the feature set may be required to enhance robustness to slight deviations in the power spectrum, particularly amongst the spectral ratio features.

Model Development

We employed a series of gradient boosted trees (XGBoost) to distinguish between EEG recordings of patients with ischemic stroke and healthy subjects. Each model was trained on a distinct subset of features, using a grid search to identify the optimal number of trees and maximum depth. Once trained, a stacked ensemble consolidated the diverse set of XGBoost models into a single classifier.

Data for training and testing was divided according to the conventional 80/20 split, with 20% of the data reserved for subsequent validation. While patients may have provided more than one recording in many instances, matching of subject IDs was performed to confirm zero overlap between training and validation sets.

To mitigate the risk of overfitting due to varying numbers of recordings per subject, two independent ensembles were trained – the first trained on strictly one recording per patient, the other learning from all available recordings.

3. RESULTS

Validation of the stacked ensemble was performed using 3-fold cross validation. To ensure an 80/20 split for both datasets with varying numbers of samples allowed per subject, it was not feasible to construct two identical validation sets. The validation set constructed using only one recording per subject had many fewer stroke cases to ensure an adequate training set size. The resulting training and validation set sizes for each partitioning are detailed in Table 4.

Our results demonstrate remarkable sensitivity and specificity in the differentiation between stroke patients and healthy subjects using EEG (Table 5, 6; Figure 4). Most notably, the ensemble trained on all possible recordings surpassed a sensitivity and specificity of >85%, a significant benchmark not yet reached by any clinical stroke scale (5). Despite a significant class imbalance, the single subject model was still able to reach a sensitivity and specificity of >85%, simultaneously. Additionally, both models were able to attain an AUC above 0.90, a challenging benchmark to achieve with the Temple dataset (16).

The individual models that comprised the top-performing stacked ensemble (duplicate subject recordings permitted) were evaluated to gain a better understanding of their ability to differentiate healthy subjects from stroke patients. The results in Table 6 indicate strong predictive power for the spectral and entropy-related features. Notably, the asymmetry-related

features displayed the weakest performance, with AUCs of 0.81 and 0.78. We suppose this could be the result of a decreased feature set.

We found that allowing multiple recordings per subject significantly enhanced model performance, particularly in terms of sensitivity. This improvement likely stems from a reduction in the existing class imbalance, achieved by including a greater number of stroke samples. Although initial concerns were raised about potential overfitting with multiple recordings from the same subjects, it was apparent that it only enhanced validation performance. Normally, multiple samples per a subject would contribute to an overfit model. However, due to the non-stationarity of EEG, small changes in environmental conditions and emotional state between recordings can introduce subtle perturbations to the signal, even if the patient's underlying pathology remained the same. These minor variations in signal increased the diversity of the dataset, thereby improving the robustness of the model.

4. DISCUSSION

Employment of EEG for stroke identification has long been of discussion. However, due to subtle differences amongst devices and recording conditions, this potential has yet to be realized. This paper demonstrates the potential of EEG in the differentiation of stroke and healthy subjects, thereby serving as an effective tool to triage and identify reperfusion-eligible patients. We present a solution trained and validated on one of the largest known clinical EEG repositories, with results demonstrating improved sensitivity and specificity compared to preexisting stroke scales.

EEG provides a direct measurement of the cerebral functional status and reveals the underlying pathophysiological processes (17). After an ischemic stroke event that causes cerebral blood

flow reduction, the metabolic and electrical activities of cortical neurons are altered (18, 19). These alterations can be observed through resting-state EEG oscillatory activity over the impacted area, demonstrating an attenuation of faster (alpha and beta) and augmentation of slower (delta and theta) frequency bands (20, 21). From our analysis, we show that the attenuation of alpha and beta rhythms is more localized, with the greatest dissimilarity appearing within the occipital region, where there is maximum alpha power. This attenuation of alpha and beta waves at the site of the occipital region could be attributable to a disruption of the posterior dominant rhythm.

Our results highlight the promise of literature-reported biomarkers for the identification of stroke from a healthy population. However, due to the non-stationarity of EEG, these features are subject to high variance across time. Therefore, careful attention must be made to ensure the time window from which these features are derived is not riddled with artifact. Future work may consider a moving average approach to smooth the feature value across the EEG recording, thereby mitigating volatility from sudden artifact.

The methods outlined in this paper introduce numerous advantages over previously published work, including a validation cohort of more than 350 subjects (78% healthy, 22% stroke) and a sensitivity and specificity greater than 85%. In future work, additional data is necessary to continue the validation of EEG in the context of stroke triage.

5. WORK WE INTEND TO DO:

While the work presented in this paper shows great promise for the detection of ischemic stroke in a variety of environmental conditions, further validation ought to be performed before the integration of these models into a clinical setting. To this point, additional work

should be performed to address any potential bias arising during training. In doing so, the model becomes more robust to the breadth of cases expected in the clinical setting.

Future directions should include evaluation of EEG measures that can discriminate between old and new infarcts, ischemic and hemorrhagic stroke, and stroke-mimicking conditions. Additional source localization methodology could also be applied to understand the regional differences in EEG measures. This can be achieved using digitized EEG leads and MRI brain scans of stroke and healthy subjects.

Table 1. Number of EEG Recordings by Patient Group

	Healthy	Stroke
Subjects (#)	1,385	374
Number of Recordings	1,521	880
Average Number of Recordings / Subject	1.18	2.35

Table 2. Demographics of Stroke Cohort

Demographic	Stroke
Age	
Mean (Std. Deviation)	63.8 (15.2)
Sex	
Male	158 (42%)
Female	192 (51%)
Not Specified	24 (7%)

Table 3. Descriptions of Features

Feature Set	Description
Spectral Ratios	Ratio of the power between slower frequencies (delta and alpha) and faster frequency bands (alpha, beta)
Band Power Difference	Simple difference in power amongst frequency bands
Relative Band Powers	Average power for each frequency band normalized by sum of all powers
Brain Symmetry Index (BSI)	Quantifies interhemispheric spectral asymmetry; Computed as the mean difference in absolute power between a sensor and its contralateral pair
Inter-Hemispheric Amplitude Ratio (IHAR)	Quantifies interhemispheric amplitude asymmetry; Revised as the difference in mean amplitude envelopes between a sensor and its contralateral pair
Sample Entropy	Quantifies degree of regularity or predictability for a time series
Hurst Exponent	Quantifies long term memory of time series by analyzing tendency of a signal to regress to its mean, or conversely, trend in a given direction

Table 4. Training & Validation Breakdown

	Single Recording Model		All Recordings Per Subject Permitted	
Cohort	**Healthy**	**Stroke**	**Healthy**	**Stroke**
Training	1,112	295	1,218	698
Validation	273	79	303	182
Total	**1,385**	**374**	**1,521**	**880**

Table 5. Summary of performances by model

Model	Sensitivity (95% CI)	Specificity (95% CI)	ROC AUC
Single Subject Recording	0.86 (0.78, 0.94)	0.86 (0.82, 0.90)	0.91
All Subject Recordings Permitted	**0.93** (0.97, 0.89)	**0.86** (0.82, 0.90)	**0.95**

Table 6. Model Performance by Feature Subset

Model	Number of Features	Sensitivity	Specificity	AUC
PSD Feature Set				
Spectral Ratios	42	0.91	0.82	0.92
Band Power Difference	31	0.83	0.77	0.90
Relative Band Powers	80	0.85	0.88	0.93
Average:	-	**0.86**	**0.82**	**0.93**
Asymmetry Feature Set				
Brain Symmetry Index	4	0.95	0.40	0.81
Amplitude Ratio (IHAR)	8	0.77	0.64	0.78
Average:	-	**0.86**	**0.52**	**0.80**
Entropy & Hurst Exponent	28	0.85	0.82	0.89
Stacked Ensemble (All Features)	**193**	**0.93**	**0.86**	**0.95**

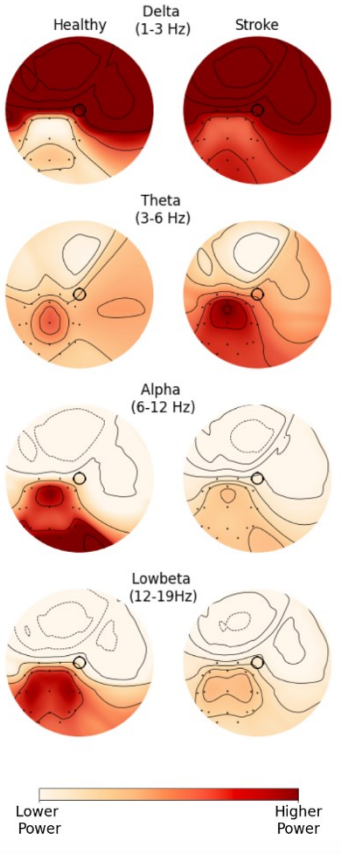


Figure 1: Topographical Plot of Frequency Band Power

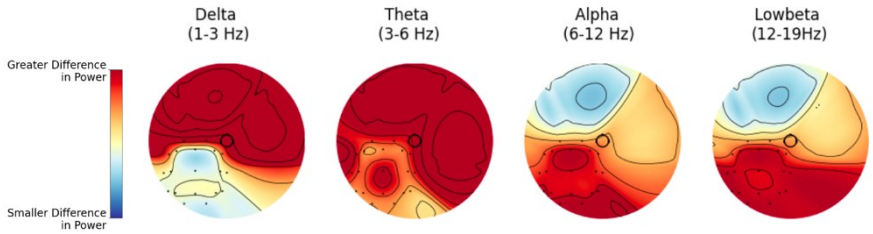


Figure 2: Topographical Display of Mann-Whitney U-Test Statistic

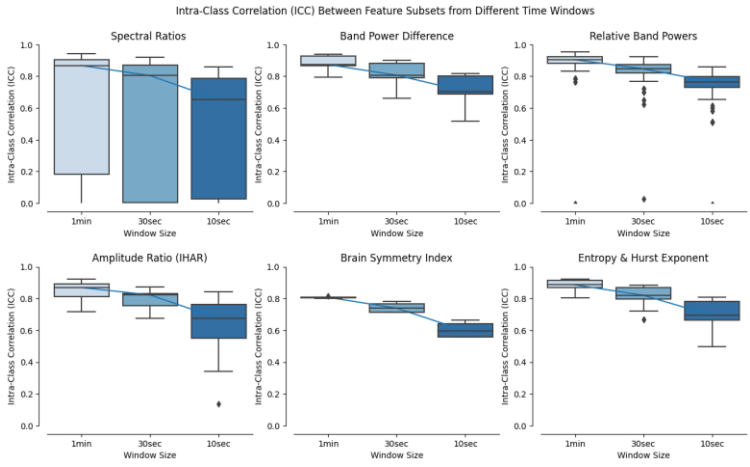


Figure 3: Intra-Class Correlation by Feature Subset

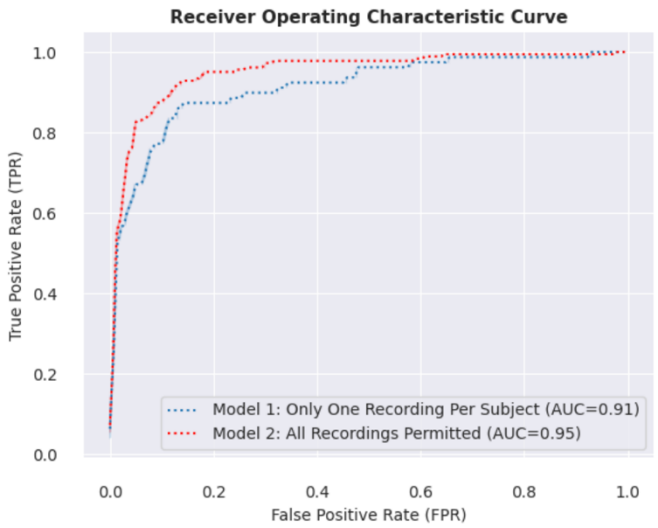
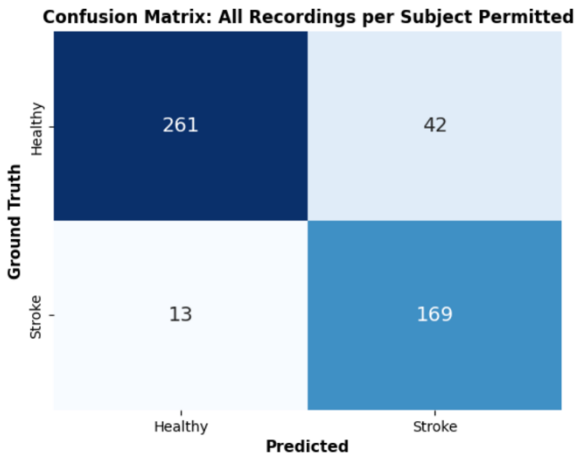
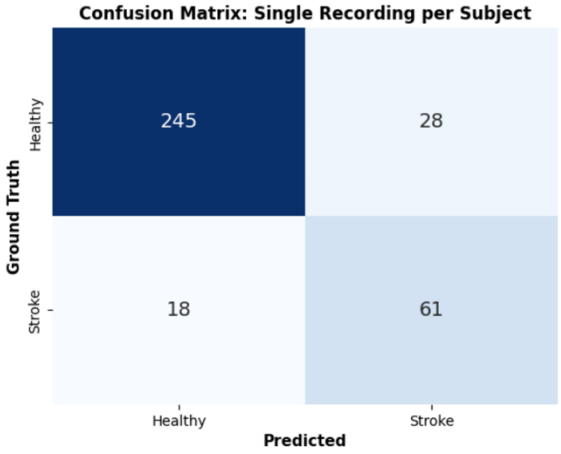


Figure 4. Model Performances by AUC

Supplementary Data:





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