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Interhemispheric Cortical Network Connectivity Reorganization Predicts Vision Impairment in Stroke

Jiahua Xu[1,2], Zheng,Wu[1,2], Andreas Nürnberger[1], Bernhard A. Sabel[2]

***Abstract*— Stroke is one of the main causes of disability in human beings, and when the occipital lobe is affected, this leads to partial vision loss (homonymous hemianopia). To understand brain mechanisms of vision loss and recovery, graph theory-based brain functional connectivity network (FCN) analysis was recently introduced. However, few brain network studies exist that have studied if the strength of the damaged FCN can predict the extent of functional impairment. We now characterized the brain FCN using deep neural network analysis to describe multiscale brain networks and explore their corresponding physiological patterns. In a group of 24 patients and 24 controls, Bi-directional long short-term memory (Bi-LSTM) was evaluated to reveal the cortical network pattern learning efficiency compared with other traditional algorithms. Bi-LSTM achieved the best balanced-overall accuracy of 73% with sensitivity of 70% and specificity and 75% in the low alpha band. This demonstrates that bi-directional learning can capture the brain network feature representation of both hemispheres. It shows that brain damage leads to reorganized FCN patterns with a greater number of functional connections of intermediate density in the high alpha band. Future studies should explore how this understanding of brain FCN can be used for clinical diagnostics and rehabilitation.**

I. Introduction

Stroke of the brain is a common cause of death and disability in the elderly, the number of which is steadily increasing. Until 2013, there were almost 25.7 million stroke survivors, 6.5 million deaths from stroke worldwide [1]. About 30-50% of the stroke cases have damage of the visual pathway which can lead to homonymous hemianopia (HH), in which the same half of the visual field in both eyes is lost. This visual field defect significantly decreases daily functional abilities and quality of life [2]. with secondary risks of falling, lose the ability to read, and anxiety and depression [3].

Graph theory-based network analysis is a fundamental methodology in neuroscience to explore brain functional connectivity (FCN) network synchronization and reorganization after a stroke. It is typically characterized by graph parameters such as strength, which is the sum of weights of links connected to one node [4].

Vision loss in the blind is a result of both, primary loss of neurons through tissue damage, and a breakdown of synchronization in brain networks [5]. Disturbed synchronization in patients with vision loss might therefore aggravate the functional consequences of reduced visual input [6]. Wang et al. [7] reported HH patients with left primary visual cortex damage have less brain functional activity than healthy subjects. Another study [8] showed that the newly forming FCN connections and compensatory connections mainly originated from the infarction area and influences contralesional cortices.

Weighted graphs with thresholds are able to reveal the level of efficiency in large-scale networks analysis [9], allow an easy extraction of meaningful information [10] compared to binary graphs. Fornito et al. [11] reported network scaling effects in human resting-state fMRI under the proportional thresholds from 5% to 40%. Buckner et al. [12] reported the hubs for adaptive task control at the proportional thresholds from 2% to 10%. Heuvel et al. [13] reported the efficiency of functional brain networks and intellectual performance from a correlation coefficient of r=0.3 to 0.5. In all these studies the authors used a rather narrow range of network density, and this could be a limitation with risks of poor or faulty interpretations. Previous graph theory studies on HH [7] [8] used scalp electrode connections without considering the network density; the stability of such patterns is still unknown. Therefore, in the present study, we characterized the cortex level's brain functional network dynamics in HH patients after a stroke, using multiscale proportional threshold-based densities for brain connectivity matrix.

Stroke biomarkers could provide a diagnostic inference for effective personalized therapy in stroke patients. Several researchers have proposed various prediction biomarkers such as fluid and tissue analysis for stroke prevention [14], [15]. Others had utilized the brain functional network connectivity to predict the impairments in stroke [16]–[18]. Moreover, deep learning technology has been widely applied in brain disease prediction [19]–[21]. Therefore, we evaluated the potential for predicting the functional loss in patients with stroke using deep learning technology through the brain network. There are many and highly sophisticated deep learning methods in the market; however, deep learning requires high computation power and colossal data size, limiting its application in brain science. Especially the use of small amounts of high-dimensional data is still facing significant challenges.

LSTM (Long Short-Term Memory) [22] was a particular type of recurrent neural network (RNN) [23] that is often used to model contextual information in natural language

[1] Jiahua Xu, Zheng Wu, Andreas Nürnberger are with data & Knowledge Engineering Group, Faculty of Computer Science, Otto von Guericke University Magdeburg, Germany {Andreas.Nuernberger}@ovgu.de

[2] Jiahua Xu, Zheng Wu, Bernhard Sabel are with institute for Medical Psychology, Medical Faculty, Otto von Guericke University Magdeburg, Germany {Jiahua.Xu, Zheng.Wu, Bernhard.Sabel}@med.ovgu.de

processing tasks. RNN models feed the information into the network only in a one-directional manner. In the present study of stroke patients, we consider both internal connections and external isolation between the lesion and intact hemisphere of the brain to evaluate if the Bi-LSTM is able to capture a better network feature presentation in bi-directional learning from both hemispheres.

We hypothesize that the Bi-LSTM can learn brain network patterns by paying specified attention to the FCN state of the lesioned as well as the intact hemisphere. We therefore implemented the Bi-LSTM model along with other traditional algorithms on the multiscale brain functional connectivity matrix to reveal brain network alteration patterns in occipital stroke patients.

Specifically, we addressed the following two questions: (i) how does the frequency band and the density of the brain connectivity matrix influence the performance of the deep neural network for predicting stroke patients, and (ii) how does the predictive performance of the model fit the characteristics of electrophysiological data using the statistics and visualization of the FCN "strength" changes in the middle occipital node.

II. Method

A. Subject

We recruited 24 Patients with partial vision loss as a result of occipital stroke(see more detail [24]) and 24 age-matched healthy subjects with normal vision or corrected to normal vision. All subjects were instructed to keep their eyes closed while resting-state EEG was recorded for the duration of five minutes (Tab I). Patient and control subjects were statistically comparable in age (p>0.05). High dense array EEG was recorded using a HydroCell GSN 128 channel net (EGI Inc.). The ethics committee of the University of Magdeburg approved the study In compliance with the declaration of Helsinki, all subjects were asked to sign a consent form.

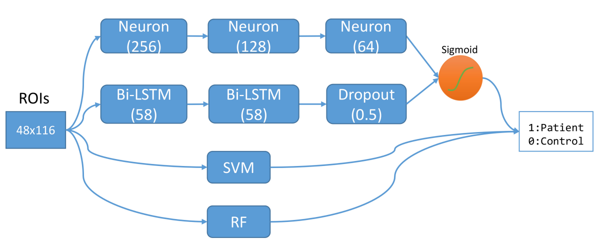

Fig. 1. We evaluated a two-layer Bidirectional LSTM (neurons: 58, 58) algorithm and compared it with other traditional algorithms such as deep forward neural network architecture with three hidden layers (neurons: 256, 128, 32), support vector machine (SVM), and random forest (RF). Data input shape (1×116) from AAL atlas. Output label was 1: patient and 0: control subject.

B. Data Prepossessing

A digital 1-145 Hz bandpass filter was applied as well as a 50 Hz notch filter. The data was down-sampled to 250 Hz and then referenced by the common average reference method. EEG recordings were segmented into 2 seconds long per epoch. Components of eye-blinks and cardiac activity were removed by independent component analysis (ICA). The signal was decomposed as six frequency bands: Delta (1-3Hz), Theta (4-7Hz), Alpha1 (8-10Hz), Alpha2 (11-13Hz), Beta1 (14-21Hz), Beta2 (22-30Hz).

TABLE I

Patient information summary

	Total	Lesion side	Age	Lesion Months
Patient	24	10 left, 14 right	58.375±10.87	40.95±39.21
Control	24	NA	57.375±10.56	NA

C. Source Reconstruction

The forward model was calculated using the symmetric boundary element method (BEM) [25]. The inverse model was calculated with a beamforming method using the partial canonical correlation method [26], which implements Dynamical Imaging of Coherent Sources (DICS) [27]. The default template for MRI was from MNI (Colin 27) at 8mm resolution [28]. The AAL-VOIs atlas (AAL) is an automatic anatomical labeling result [29], which includes 120 structure definitions, and 116 were used in this study.

D. Brain Connectivity and Threshold

Functional connectivity was based on the statistical synchronization to quantify the interaction between different brain region pairs [30]. Here we used the imagery part of coherence [31], shown in equation (1), which is insensitive to false connectivity arising from volume conduction to measure the functional connectivity with resting-state EEG data.

$$icoh_{(f,t)} = |im\left(\frac{\sum_{n=1}^{N} S_1^n(f,t) S_2^{n*}(f,t)}{\sqrt{\sum_{n=1}^{N} |S_1^n(f,t)^2| \sum_{n=1}^{N} |S_2^n(f,t)^2|}}\right)| \tag{1}$$

where $S_1^n(f,t)$ and $S_2^{n*}(f,t)$ are the frequency-decomposed EEG data from two specific regions. We adopted a parcellation scheme with the AAL atlas and average the connectivity values between sets of dipole pairs that belong to a given pair of parcels. Finally, the connectivity matrix (116×116) was sparsed from density 0.1 to 1 per frequency band for patients and controls. All self-connections were removed before analysis, which means only$[0.1 \sim 1]$ strongest weight edges were kept for each subject in both groups consistently. In this case, the density defined as the proportion of existing edges out of all possible edges was equal for each graph per subject [32]. Fixing the probability for an edge also excludes the criteria of Erdős-Rényi random networks for group analysis [33].

E. Evaluation method

A deep neural network (DNN) is an artificial neural network (ANN) with multiple layers between the input and output layers [34]. The hidden layer and activation functions can improve the expressive ability. In this paper, we implemented a two hidden layer (58, 58) Bi-LSTM model and a three hidden layers (256, 128, 32) deep forward network with 'RELU' activation function. The support vector machine (SVM) and Random forest (RF) were referred as the baseline shown in Fig. 1. Brain node strength was calculated per frequency and density, then we proposed three feature extraction methods: Model I): The node strength of control subjects between the left and right hemispheres was pooled. The brain of the right stroke patient was flipped so that only the lesion hemisphere and intact hemisphere were showed. Model II): The controls were not pooled, and the patient data was flipped. Model III): The controls were not pooled, and the patient data was not flipped (see Tab II).

F. Training the model

All training sessions were implemented in Google Colab, Sklearn, and Keras, 48 subject data was shuffled before a three-folder cross-validation in the training session. For both Bi-LSTM and DNN, we took Adam as the optimizer and binary-cross entropy as the cost function. The performance was evaluated with three metrics: overall accuracy, sensitivity, and specificity. A non-parametric Mann- Whitney U-test was performed between the lesion hemisphere and the control hemisphere and between the intact hemisphere and control hemisphere. Data prepossessing, source reconstruction, and brain connectivity were conducted with the Fieldtrip toolbox [35].

III. Result

A. Model performance

We evaluated Bi-LSTM, DNN, SVM, and RF to scout for appropriate prediction biomarkers (Frequency bands or network density), which can identify the presence of vision impairment in patients with occipital stroke. As shown in Tab II, the DNN yielded the highest accuracy (81%) in model I; however, the sensitivity (67%) was relatively low and the specificity was significantly higher (96%). This demonstrates that pooling the left and right hemispheres for the controls may lead to an over-fitting in testing data. The same phenomenon appeared in SVM performance. The Bi-LSTM shows a balanced performance between sensitivity (70%) and specificity (75%) with an overall accuracy of 73% in model II, suggesting that flipping the hemisphere could enhance the feature patterns learning during training. As shown in Fig. 3, the log loss of model II shows the Bi-LSTM demonstrated the ability to learn the feature patterns and continuously reduce losses. For RF, the result is not satisfied with worst performance.

B. Biomarker in Brain network

Stroke biomarkers can be used as a guiding tool for more effective personalized therapy [14], and help improve the diagnosis of stroke and determine the cause of stroke [15]. Unlike the traditional approach, we aimed to find the characteristics representing the network reorganization after a stroke with a bi-directional LSTM algorithm. This algorithm has been used for natural language processing for a long time. Here, we explored the two-directional feature

TABLE II

Final peak performance of the evaluated models

	Model	Pooled Control	Flipped Patient	Accuracy	Sensitivity	Specificity
SVM	I	Yes	Yes	67%	58%	75%
	II	No	Yes	**73%**	63%	**83%**
	III	No	No	67%	54%	70%
RF	I	Yes	Yes	63%	54%	70%
	II	No	Yes	63%	58%	63%
	III	No	No	60%	63%	41%
DNN	I	Yes	Yes	**81%**	67%	**96%**
	II	No	Yes	70%	75%	67%
	III	No	No	67%	75%	58%
BiLSTM	I	Yes	Yes	63%	58%	67%
	II	No	Yes	**73%**	**70%**	**75%**
	III	No	No	63%	63%	63%

learning efficiency from intact and lesion hemispheres. As shown in Fig. 3, the peak accuracy was achieved in the low alpha band from density 0.3 to 0.5 with Bi-LSTM. The result is compatible with the hypothesis that brain network reorganization in the low alpha band after a stroke can help identifying occipital stroke patients. The network threshold should be taken into account for brain network analysis or biomarkers prediction in neurological disease.

In our patients, the middle occipital lobe area is most affected by ischemic stroke (Posterior cerebral artery infarcts). To further confirm the patterns from the network characteristics, we specifically selected the middle occipital lobe for further statistical analysis. As shown in Fig. 4, the strength of the alpha band in both lesion and intact hemisphere was found significantly lower than in controls for a density$>$0.3, which is consistent with our prediction result.

IV. Discussion

A correct diagnosis of ischemic stroke and its causes are essential to treat and prevent stroke [15]. While MRI images used in the clinic to identify the lesion location are structurally meaningful, they provide no information about the functional state of the tissue at or around the lesion site (locally) or in other brain regions (globally). This can only be achieved with EEG recordings that provide electrophysiological information about the activity of neurons and their interactions. Therefore, assessing brain network reorganization in a quantitative manner offers a new “functional” dimension to characterize brain damage and recovery. Traditional biomarkers such as blood, other body fluids, or tissues have been proposed to predict neurological disease states physiologically [14]. In contrast, the present study aimed to find a 'biomarker' based on multiscale brain network and deep neural network. We evaluated pattern learning efficiency of Bi-LSTM with bidirectional vector from two hemispheres. The result demonstrates that the brain node strength in the low and high alpha band could be utilized for predicting functional (vision) loss in occipital stroke patients, and the Bi-LSTM achieved an excellent performance which was more specific and effective than other traditional algorithms of hemisphere pattern learning. The

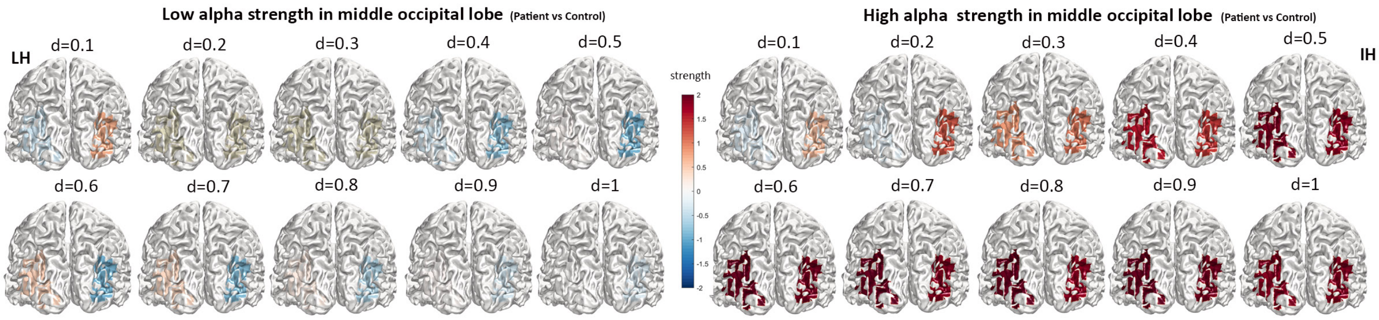

Fig. 2. The plot shows the low and high alpha band strength distribution from density 0.1 to 1 in the middle occipital lobe. This dynamic change of network properties shows that the reorganization of the brain after the damage is mostly based on the formation of massive weak connections in the high alpha band. In contrast, the low alpha band did not show massive connections. From the evaluation models, SVM learned feature patterns from the high alpha band, and Bi-LSTM learned low alpha feature patterns and achieved a balanced performance between sensitivity and specificity.

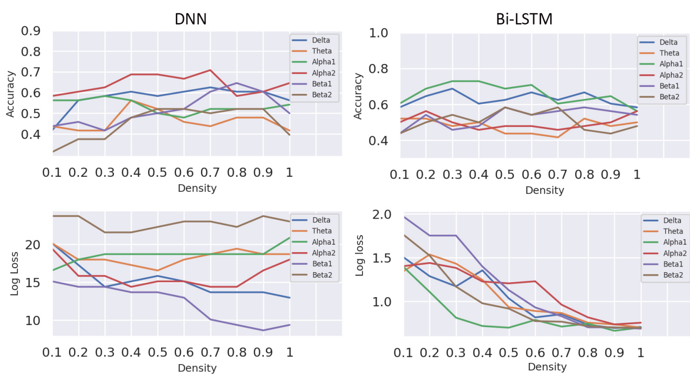

Fig. 3. Compared to the Bi-LSTM, the DNN shows a slice better performance in model I in the high alpha band. However, here the log loss is relatively stable and higher than the Bi-LSTM. Bi-LSTM shows a balanced performance between sensitivity (70%) and specificity (75%), with an overall accuracy of 73% in model II in the low alpha band. Eliminating the structure influence of individual algorithms, the result suggests that flipping the patient's hemisphere could enhance the feature pattern learning, while the controls should not be pooled.

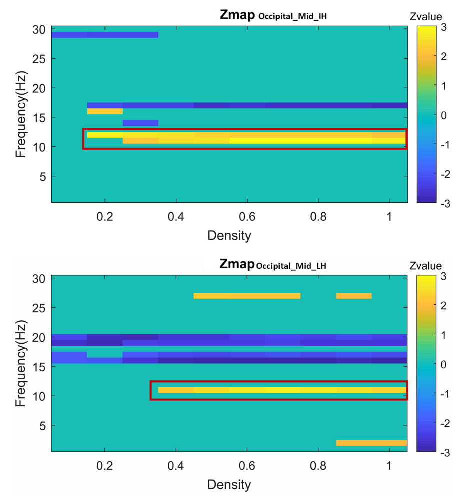

Fig. 4. Left part: Z-value distribution between the lesion /intact hemisphere and the control hemisphere at the middle occipital lobe. Significant patterns show that both intact hemispheres have higher strength in the alpha band (8-13 Hz) than controls when selecting a density>0.3 (red-box). The strength in the low beta band (14-21) of both lesion and intact hemisphere was lower than the controls.

result from Model II illustrates that hemisphere flattening in unilateral stroke patients and no-pooling in controls has a palpable classification performance to discriminate between visually impaired stroke patients and normal subjects.

Alpha phase synchronization is known to relate to different behavioral states and neuronal effects of visual-spatial attention [36]. With the present study we confirmed the role of the high alpha band in visual processing, because in this frequency band brain damage leads to reorganized FCN patterns with a greater number of functional connections of intermediate density(see Fig. 2). Future studies should explore how this understanding of brain FCN can be used for clinical diagnostics and rehabilitation. This new perspective is consistent with earlier findings that both low and high alpha brain network alternation are critical in brain network reorganization of stroke patients [7]. Our future studies will evaluate with if and how the strong connections from the lesion side can handle information processing after a stroke; and how the contralateral, "intact", functional regions might help to compensate for the loss of vision.

More generally speaking, deep learning technology with optimized structures can help extract functionally relevant parameters by using FCN pattern characterization without predefined features. Bi-LSTM achieved a more balanced performance (in both accuracy and log loss) than other methods. Considering the mechanism of Bi-LSTM in natural language processing, we propose that the Bi-LSTM method is a useful procedure for capturing brain network states of the lesion and intact hemisphere. Integration of bidirectional data input (intact vs. lesioned hemisphere) though LSTM cell can enhance the performance and stability of the model. Although the model's final performance did not reach a high accuracy rate for all models in this study, we believe that the expected results can be obtained using a larger data sample with Bi-LSTM. Moreover, the performance can inspire us into the understanding of brain network reorganization after an occipital stroke in the clinical context of diagnosing vision loss and predicting its recovery potential.

V. Conclusion

This study evaluated the potential of predicting vision impairment in stroke patients with deep neural networks and multiscale brain networks. The prediction model and statistical analysis results show that brain node strength in the low and high alpha band under specific density could be a predictor to characterize brain network reorganization in stroke patients. The Bi-LSTM gained a balanced performance between sensitivity and specificity, proving its feature learning capacity for hemisphere feature extraction. Further investigation are needed to extend this algorithm with more data samples and optimized network structure. In the future, these results may inspire other to gain more insight in stroke clinical diagnostics and interventions, and it highlights the value of Bi-LSTM in functional predictions of brain diseases.

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