Deep Convolutional Neural Networks for the Accurate Identification of High-Amplitude Stereotypic Epileptiform Seizures in the Post-Hypoxic-Ischemic EEG of Preterm Fetal Sheep

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***Abstract*—Neonatal seizures after birth may contribute to brain injury after an hypoxic-ischemic (HI) event, impaired brain development and a later life risk for epilepsy. Despite neural immaturity, seizures can also occur in preterm infants. However, surprisingly little is known about their evolution after an HI insult or patterns of expression. An improved understanding of preterm seizures will help facilitate diagnosis and prognosis and the implementation of treatments. This requires improved detection of seizures, including electrographic seizures. We have established a stable preterm fetal sheep model of HI that results in different types of post-HI seizures. These including the expression of epileptiform transients during the latent phase (0-6 h) of cerebral energy recovery, and bursts of high amplitude stereotypic evolving seizures (HAS) during the secondary phase of cerebral energy failure (~6-72 h). We have previously developed successful automated machine-learning strategies for accurate identification and quantification of the evolving micro-scale EEG patterns (e.g. gamma spikes and sharp waves), during the latent phase.**

The current paper introduces, for the first time, a real-time approach that employs a 15-layer deep convolutional neural network (CNN) classifier, directly fed with the raw EEG time-series, to identify HAS in the 1024Hz and 256Hz down-sampled data in our preterm fetuses post-HI. The classifier was trained and tested using EEG segments during ~6 to 48 hours post-HI recordings. The classifier accurately identified HAS with 98.52% accuracy in the 1024Hz and 97.78% in the 256Hz data.

Clinical relevance—**Results highlight the promising ability of the proposed CNN classifier for accurate identification of HI related seizures in the neonatal preterm brain, if further applied to the current 256Hz clinical recordings, in real-world.**

I. Introduction

Perinatal complications of a difficult labor can cause oxygen deprivation leading to hypoxia-ischemic encephalopathy (HIE), at birth. A severe HIE insult evolves over time from early post-HI recovery over hours, days and weeks post-insult, causing significant grey and white matter injury [1]. A latent phase of recovery of cerebral oxidative metabolism is followed by a secondary loss of metabolism [1]. We have shown in our experimental chronically instrumented preterm fetal sheep model that micro-scale EEG events, such as sharp waves, evolve during the latent phase and are predictive of neural outcome (Figure 1) [1-4]. The secondary phase is often characterized by the appearance of high-amplitude stereotypic evolving seizures (HAS) (see Figure 1) [5, 6]. Clinical studies have shown that seizures can occur after preterm birth, although many may be subclinical [7], and under some conditions may play a role in causing or exacerbating brain injury, impairing neurodevelopment and may contribute to later life risk of epilepsy [8-11]. Currently, however, the data about preterm seizures are surprisingly limited and it is increasingly recognized that here is a need to improve detection of and characterization of seizure patterns in preterms to improve our understanding about when they occur, their contribution to injury and for the development of treatments [10-12].

Reliable automated analysis of EEG activity will assist in clearly identifying preterm seizure activity. We have previously developed successful automated machine-learning strategies for the accurate identification of latent-phase micro-scale events, such as spike transients [2, 13-15], sharp waves [4, 16-19] as well as stereotypic evolving micro-scale seizures (SEMS); which are rolling waveforms in delta band [20], in the EEG of preterm fetal sheep after HI. We have also recently developed an accurate 17-layer deep 2D-CNN sharp wave classifier that uses wavelet scalograms of the ECoG segments to extract robust feature maps over a wide spectral-range (WS-CNN classifier) [18].

This paper, for the first time, introduces an accurate real-time approach that uses a deep one-dimensional convolutional neural network (CNN) seizure classifier in preterm sheep HI data. This has been used to identify high-amplitude stereotypic seizures in EEG 1024Hz and 256Hz down-sampled EEG data in preterm fetal sheep post-HI. The paper describes how the raw EEG segments from more than 81 hours of post-HI recordings can be used to robustly train a 15-layer deep 1D-CNN classifier to accurately identify HAS from background activity and high-amplitude noise.

II. Methods

A. Data collection

The animal studies and procedures in this paper were approved by the Animal Ethics Committee of the University of Auckland, under the Animal Welfare Act (1999) of New

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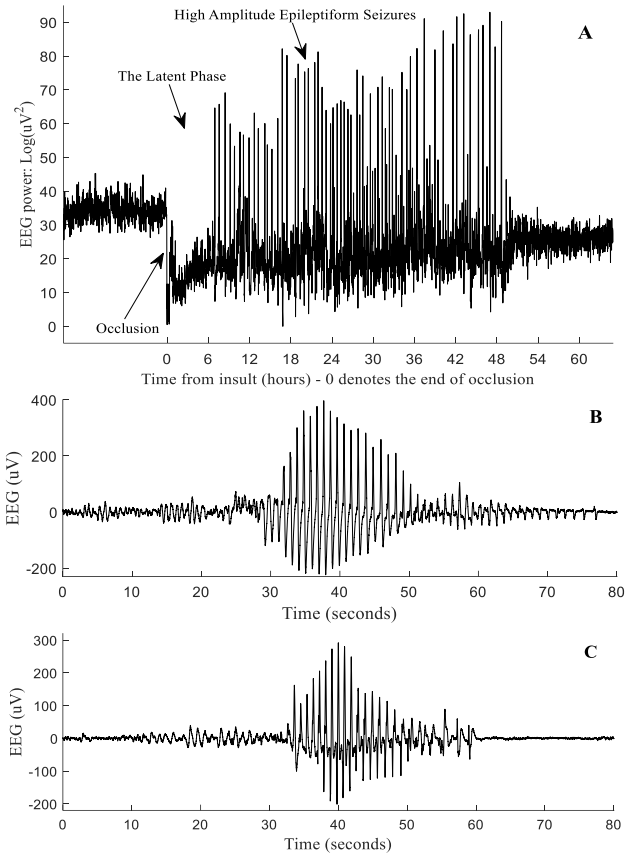

Figure 1. (A): Post HI-insult EEG power activity containing high-amplitude stereotypic seizures from asphyxicated preterm fetal sheep. (B-C): Examples of the HAS in the training and test sets of sheep #1 & #2.

Zealand. Two fetal sheep were studied for this paper at 0.7 of gestation; fetuses at this age have brain maturation equivalent to a preterm human brain of around 27-30 weeks of gestation [21]. The animal management and surgical procedures have been described previously [5]. Briefly, under anesthesia we instrumented the fetus with arterial catheters post-surgical monitoring of fetal cardiovascular function and for blood sampling, as well as placement of a silicone occluder around the umbilical cord to induce an acute HI insult. For EEG recordings, electrodes made in-house using Cooner Wire (Cooner Wire, Chatsworth, CA, USA), were placed on the dura of the fetal parasagittal cortex and covered and secured in place. A reference electrode was placed over the occiput [5]. Technically, this placement provides an electrocorticogram recording (ECoG), and the direct placement on the cortex provides a clear signal from which useful signal components (e.g. gamma band spectrums) can be derived [22]. From here, we refer to ECoG for the signal.

Following instrumentation, fetuses are returned to the uterus, and ewes and fetuses given 4-5 days to recovery. Fetuses then underwent an acute HI insult of 25 min of complete umbilical cord occlusion titrated by cardiovascular and blood gas variables as previously described [5]. ECoG data were recorded continuously pre and post-HI from both left and right hemispheres of the brain. We collected over 81 hours of ECoG data. The entire bursts of high-amplitude epileptiform seizures within the 81 hours recordings were manually labelled and used in the analysis. We used 66 hours of post-HI data from fetal sheep #1 to train and validate the classifier and 15 hours of post-HI recordings from fetal sheep #2 was used to test the net.

B. High-Amplitude Stereotypic Epileptiform Seizures

HAS in preterm and full-term neonates are defined as repetitive electrographic EEG waveforms with a rhythmic and stereotypic evolving nature [23]. HAS events with similar characteristics on ECoG recordings have been reported by us in previous fetal sheep experiments (see Figure 1, B-C) [5, 6]. HAS have been classified as ongoing bursts of very high amplitude EEG patterns that last for a minimum of 10 seconds that emerge in varying large amplitudes as the injury evolves [5, 6]. For consistency with clinical definitions as well as our previous studies, similar criteria were used to annotate the data.

B. Pre-processing

The original fetal ECoG recordings were initially low-pass filtered using a 6th order anti-aliasing Butterworth filter. Data were also high-pass filtered using a first-order filter with 1.6Hz and 512Hz cut-off frequencies and digitized at a 1024Hz sampling frequency rate. Data were then amplified (×10,000 gain) and finally extracted into Matlab for seizure analysis. Data were initially normalized and zero-meaned and ECoG segments of 4 minutes length were selected from the 1024Hz raw ECoG signals to shape input vectors. The chosen input size of the ECoG segments assures that the input data covers HAS with longer lengths. Data were also down-sampled by a factor of 4 to generate the 256Hz datasets. ECoG segments were directly fed into a 15-layers deep one dimensional (1D) convolutional network (CNN) for training, validation, and testing. For the 1024Hz data, ECoG time series of length 245760 ×1 samples (4 min) were chosen to create the training/validation set. The length of ECoG segments in the 256Hz down-sampled data was reduced to 61440 samples. To generalize the validity of the classifier and fortify outcomes, the original data were not further de-noised. This facilitates with the training of the classifier using a more challenging data that is closer to near-real situations. Data were labeled manually by an expert (HA). The deep 1D-CNN classifier was trained, validated, and tested using a total of 747 ECoG segments, including 83 intervals containing HAS and 664 non-HAS epochs. The algorithm was developed, trained, and tested in Matlab® on a single workstation computer: Intel® Core™ i7-7700 CPU 3.60GHz, 4 cores processor with 16GB RAM.

C. The proposed deep 1D-CNN classifier

Convolutional neural networks are the enhanced deep-learning structures with demonstrated ability in signal and image processing [24]. Due to their proven capability, CNNs have been recently applied to clinical data for neonatal seizure recognition in multi-channel EEG recordings [25, 26]. Following our successful use of WS-CNN [18], and because of the strong capability of the convolutional classifiers, this study introduces, for the first time, a one-dimensional CNN architecture for the identification of HAS

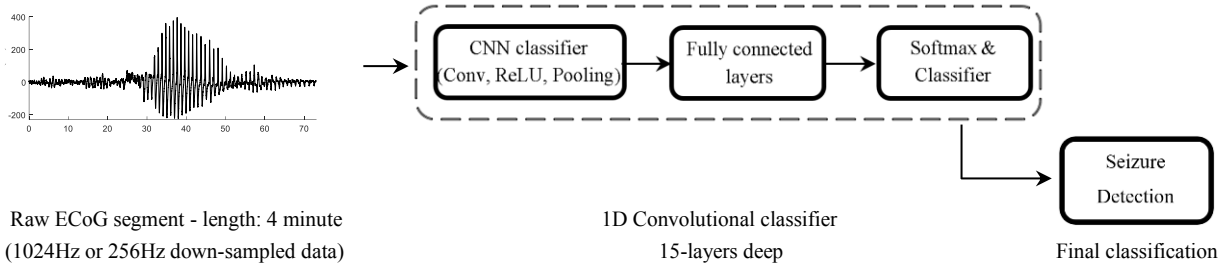

Figure 2. The schematic of our proposed 1D-CNN classifier.

in post-HI ECoG. This was initially done by by-passing the WS generating block of our previous WS-CNN pattern classifier in [18] and feeding the 1D-CNN directly with the raw ECoG segments in the form of one-dimensional time-series. The 1D-CNN takes the input time-series (245760×1), and produces internal feature-maps for classification. A total of six convolutional (with rectified linear activation units (ReLU) after each convolutional layer), six max-pool and three fully connected layers (total of 15 layers), and a final softmax and classification layer were used for final reasoning. The architecture of the proposed 1D-CNN classifier is detailed in Table I. Figure 2 also represents a graphical demonstration of the proposed approach.

Here, we used a stochastic gradient descent with momentum (SGDM) strategy to update the weights and bias parameters. Learning rate, α, and momentum, γ, parameters were initially set to 0.01 and 0.9, respectively, to minimize the loss function. Due to the satisfactory high-performances, the parameters (α and γ) were not further tuned. 66 hours of post-HI recordings from the 1st fetal sheep (sheep #1), with a random data distribution of 80% and 20%, were used for training and initial validation of the classifier, respectively. Sheep #1 was selected for training due to possessing a higher number of HAS. 15 hours of data from the 2nd fetal sheep (#2) were then used to test the classifier on an unseen dataset. The classifier was trained over a total of 50 epochs. The original 1024Hz data was also down-sampled to 256Hz to assess the performance ability of the 1D-CNN approach in near-clinical situations.

TABLE I. THE ARCITUCHURE OF THE PROPOSED 1D-CNN CLASSIFIER

Layers	Type	No. of Neurons (Output)	Kernel size	Stride	No. of Filters
0-1	Conv.	241665×1	[4096 1]	1	4
1-2	Max_pool	120832×1	[3 1]	2	
2-3	Conv.	118785×1	[2048 1]	1	6
3-4	Max_pool	29696×1	[5 1]	4	
4-5	Conv.	28673×1	[1024 1]	1	8
5-6	Max_pool	7168×1	[5 1]	4	
6-7	Conv.	6657×1	[512 1]	1	10
7-8	Max_pool	1664×1	[5 1]	4	
8-9	Conv.	1153×1	[512 1]	1	18
9-10	Max_pool	288×1	[5 1]	4	
10-11	Conv.	33×1	[256 1]	1	24
11-12	Max_pool	8×1	[5 1]	4	
12-15	Fully_connected	384			
	Fully_connected	10			
	Fully_connected	2			

III. RESULTS

Results of the confusion matrices using the proposed 15layers deep 1D-CNN classifier are represented in Table II. The deep-trained 1D-CNN precisely identified bursts of high-amplitude stereotypic seizures in 1024Hz sampled ECoG with 98.52% overall accuracy (AUC: 0.977). The accuracy of the classifier was also high, with only a negligible drop within the margin of error, at 97.78% for the 256Hz down-sampled data (AUC: 0.929). Figure 3 illustrates the ROC plots of the proposed classifier for both 1024Hz and 256HZ data. Results indicate that the 1D-CNN classifier can robustly identify ECoG segments that include high-amplitude seizures from ECoG background activity and noise, both in the high-resolution 1024Hz ECoG and 256Hz down-sampled data. The proposed 1D-CNN classifier, which compared to our WS-CNN method [18] uses a computationally-lighter strategy, was able to classify HAS from non-HAS epochs with 100% accuracy at the training and validation levels for both 1024Hz and 256Hz data. Computation-wise, the algorithms ran much faster when the deep 1D-CNN classifier was applied to the 256Hz down-sampled data; therefore, the negligible 0.74% lower performance from the 256Hz dataset (that falls well within the margin of error) can be compromised for speed. The minimal number of missed (False Negative) and wrong (False Positive) detections at the test level (unseen data) further confirms the capability of the proposed deep CNN classifier in building robust feature maps for reliable identification of seizure, if further applied to the current 256Hz clinical recordings, in real-world.

IV. CONCLUSION

This paper, for the first time, introduced an accurate real-time 15-layers deep CNN classifier, directly fed with the raw HI ECoG time-series, to identify high-amplitude stereotypic epileptiform seizures in 1024Hz and 256Hz down-sampled data from preterm fetal sheep obtained *in utero*. The work has impact by demonstrating the promising possibility to accurately identify ECoG segments containing bursts of high-amplitude seizures from background activity and large-amplitude noise, in the post-HI recordings. The proposed 1D-CNN classifier was able to reliably identify ECoG segments containing high-amplitude seizures with considerably high-accuracies of 98.52% and 97.78% for the 1024Hz and 256Hz down-sampled data, respectively, tested over more than 81 hours of experimental data. The validity of these preliminary results should be further investigated in

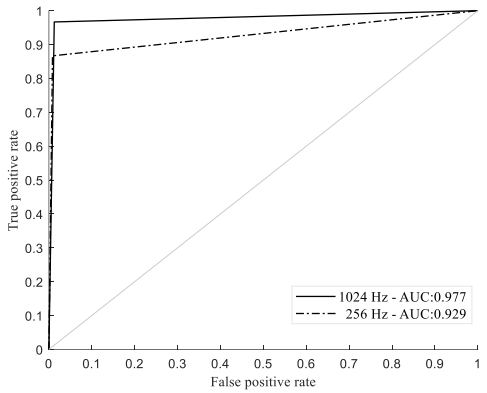

Figure 3. ROCs and the corresponding AUCs for the 15-layers 1D-CNN High-Amplitude Stereotypic Seizure detector in 1024Hz & 256Hz data

TABLE II. PERFORMANCE MEASURES OF THE 1D-CNN CLASSIFIER ON 1024HZ AND 256HZ DOWN-SAMPLED DATA

	Data	TP hits	TN hits	FP hits	FN hits	Sensitivity (%)	Selectivity (%)	Precision (%)	Accuracy (%)
1024Hz data	Train	42	339	0	0	100	100	100	100
	Val	11	85	0	0	100	100	100	100
	Test	29	237	3	1	96.67	98.75	90.63	98.52
256Hz data	Train	42	339	0	0	100	100	100	100
	Val	11	85	0	0	100	100	100	100
	Test	26	238	2	4	86.67	99.17	92.86	97.78

a more detailed study using other deep-learning structures (e.g. with shallower depth) on a bigger dataset. Further, due to working with one-dimensional inputs, the developed algorithm is computationally less-expensive compared to our previous WS-CNN classifier. This an important step forward towards the real-time identification and quantification of EEG seizures in the current experimental and clinical recordings that are generally sampled at lower frequency rate of 256Hz.

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