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Research article

Matching the ripple-wave to the episodic memory
－A case study of rat

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Abstract

Hippocampus in the brain makes an important role in the formation of memories. However, it is not clear the different episode memories concern with what kind of activity pattern of hippocampus. In this study, the multi-unit activity (MUA) of hippocampus CA1 neurons in male rats experiencing one of 4 kinds of events was analyzed by a deep learning method. The events may occur episode memories included restraint stress, contact with a female rat, contact with a male rate, and contact with a novel object. The deep learning method is a hybrid machine learning model composed by a convolutional neural network (CNN) and support vector machine (SVM). Four kinds of episodic memories including restraint stress, contact with a female rat, contact with a male rate, and contact with a novel object. Details of MUA recording can be found in "A possible coding for experience: ripple-like events and synaptic diversity" by Ishikawa, Tomokage, and Mitsushima (doi: https://doi.org/10.1101/2019.12.30.891259). The event-related sharp waves and ripples were recognized with 89.45% accuracy in the experiment. Additionally, by the extraction of feature of ripple signals using Grad-CAM and classification of those patterns using Principal Component Analysis (PCA), the difference of the MUA concerning to 4 kinds of episode memories was shown.

Keywords: episodic memory, ripple-wave, machine learning, convolutional neural network (CNN), support vector machine (SVM)

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1. Introduction

Hippocampus plays an important role in processing episodic memory. The different patterns of firing activity of CA1 area neurons in hippocampus corresponds to the different high order functions of the brain such as memory, association, planning, action decision, etc[1-5]. Sharp wave ripples, which appear in local field potential (LFP) in animal brains, concern with memory consolidation and planning[1, 4], and memory retrivals[2]. The generation mechanism of sharp wave ripples[3] and the relationship between events experienced by the brain and sharp wave ripples in CA1 area of hippocampus are investigated recently [5].

Since individual neurons can process binary data using all-or-none principle[16], we recorded multiple-unit firing activity (MUA: 300 - 10k Hz) to record as ripple-like firing events[5] instead of the sharp wave ripples. Here we investigated two issues of the ripple-like firings: the first one is how the state-of-the-art machine learning method can recognize the specified patterns corresponding to the

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different events which are a rat experienced; the second one is to extract specific aspects of the firings in the encoding process of episodic memory processing in different experiences. For the first problem, a deep learning model, which is a composition of convolutional neural network (CNN) and support vector machine (SVM), is adopted to classify 4 kinds of time series data of multi-unit activity (MUA) corresponding to episodic memories of a male rat: restraint stress (restraint), contact with a female rat (female), contact with a male rat (male), and contact with a novel object (object). For the second, Grad-Cam[6] is utilized to find the characteristic patterns of ripple-like firings related to the different events. Additionally, the correlations of ripple-like firings among the 4 episodic memories are brought out by the combination of Fourier transform and principal component analyze (PCA). According to the results of recognition experiment and MUA pattern analysis, this study suggests that it is available to recognize episodic memories by MUA data, and vice versa.

2. Related Works

To classify the pattern of EEG signals, methods such as linear discriminant analysis (LDA), support vector machine (SVM), artificial neural networks (ANN), fuzzy inference systems, Bayesian graphical network (BGN), etc. have been proposed[7, 8]. In our previous work, receiver operating characteristic (ROC) analysis method was adopted to extract event-evoked time series data of EEG signals, and the experiment results showed the effectiveness of our method[9, 10].

Recently, deep learning models such as convolutional neural networks (CNN) are energetically developed for their outstanding performance comparing with the conventional methods. Tang, Li, and Sun proposed an original 5-layer CNN model which lack of pooling layer to classify the different EEG patterns of motor imaginary[11]. Schirrmeister *et al.* designed kinds of CNNs which input raw EEG signals[12]. In fact, it is very important to extract the feature of the input data for any classifier, and features of EEG signals used to be given by handcrafted process. For the ability of feature extraction of CNNs, it is considerable to combine CNN with other classifies such as multi-layer perceptron (MLP), SVM, etc. Recently, we proposed kinds of hybrid EEG recognition methods[13] such as SVM with MLP (MLP+SVM), SVM with CNN (CNN+SVM), SVM with stacked auto-encoder (SAE) (SAE+SVM), SVM with CNN and MLP ((CNN+MLP) + SVM), and CNN without pooling layer[11] with SVM. Our experiment results, which were classification accuracies of a benchmark data given by Colorado State University[14], and BCI competition II data[15], showed the priorities of the proposed hybrid methods for EEG signal recognition, specially, the case of CNN with SVM outperformed. So the deep learning model composed by CNN with SVM is adopted in this study.

3. A Hybrid Model used in MUA Pattern Recognition

According to the previous investigation as described in Section 2, machine learning methods such as LDA, CNN, SVM, SAE, etc., are useful to classify the pattern of MUA and find the episodic memory according to the pattern of MUA. Specially, the hybrid model composed by a convolutional neural network (CNN) and support vector machine (SVM) proposed in our previous work for EEG signal recognition[13] is available to be applied to the recognition of MUA in this study. In this section, the hybrid model is introduced in detail. To specify the feature of episode-related MUA signals, Gradient-weighted Class Activation Mapping (Grad-CAM) [6], is also adopted in this study, and it is introduced in the end of this section.

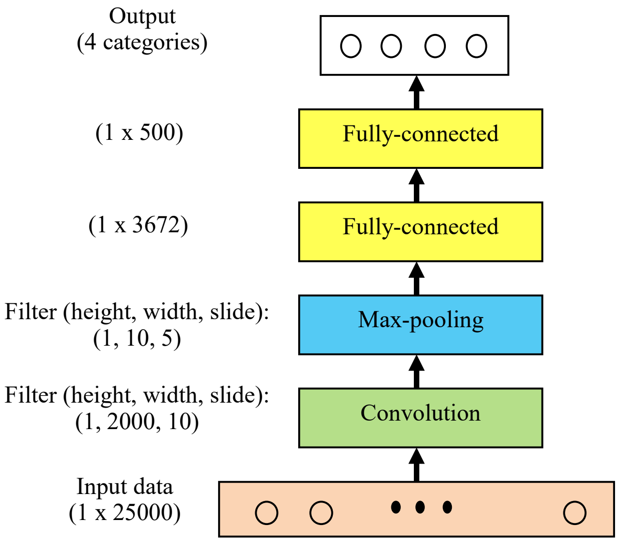


Figure 1. An architecture of a shallow CNN.

3.1. CNN

As a computational visual information processing model, the convolutional neural network (CNN) has been widely used in object recognition, image classification, signal processing and other fields. There are many kinds of CNNs have been proposed since 2010s, and a simple architecture of CNN used in this study is shown in **Figure 1**. There are two reasons of the shallow architecture of CNN used here: 1) The number of MUA patterns to be recognized is only 4 classes in this study; 2) It is more convenient to analyze the feature of these patterns by class activation map (Grad-CAM)[6] by a shallow CNN.

For an input vector $x(x_1, x_2, \ldots, x_i, \ldots, x_N)$, the output of a neuron $k = 1,2,\ldots,K$ of output layer y_k, and units $z_l^{(2)}, z_m^{(1)}, u_n, z_{ji}$ of other 4 layers are given as following equations.

$$y_k = f(\sum_{l=1}^{L} w_{kl} z_l^{(2)} + b_k) \quad (1)$$

$$z_l^{(2)} = f(\sum_{m=1}^{M} w_{lm} z_m^{(1)} + b_l) \quad (2)$$

$$z_m^{(1)} = f(\sum_{n=1}^{N} w_{nj} u_n + b_m) \quad (3)$$

$$u_n = \max_{(i,j)\in P_n} z_{ij}, \quad (4)$$

$$z_{ji} = f(\sum_{p=1}^{H} \sum_{q=1}^{W} \quad w_{pq} x_{i+p,j+q} + b_{ji}) \quad (5)$$

where $w_{kl}, w_{lm}, w_{nj}, w_{pq}$ are weights of connections between units, b_k, b_l, b_m, b_{ji} are biases, P_n is the pooling size, H, W indicate the height and width of the receptive field when the input is 2-D images. $f()$ is a ReLU active function.

The modification of parameters of CNN is given by the gradient of mean squared error (MSE) of output (error back-propagation learning algorithm (BP method)) and the derivation and learning algorithm is omitted here for there are many open-source tools including solution method of CNNs.

3.2. SVM

Support vector machine (SVM) proposed by Vapnik in 1963 and 1992 is the most popular machine learning model for classification and regression analysis of data science after the boom of MLP. As a supervised learning method, SVM aims at finding a hyper-plane or set of hyper-planes to separate high-dimensional data $\mathbf{x}$ to different classes. Mathematically, the classifier is given by a kernel function $\phi(\mathbf{x})$ (usually radial basis function) to map the input data to a vector space with higher dimensionality:

$$f(\mathbf{x}) = sign(\mathbf{w}^{\mathrm{T}}\phi(\mathbf{x}) + b) \tag{6}$$

The detail of method to find parameters $\mathbf{w}$ and b is omitted here for there are many open source tools including solution method of SVM.

The original SVM is a classifier for two-class data. For multiple classes data, for example, class A, B, and C, 3 SVMs need to be used: SVM1 for A and B, SVM2 for B and C, and SVM3 for A and C. The final classification results of unknown data are decided by the votes of 3 SVMs.

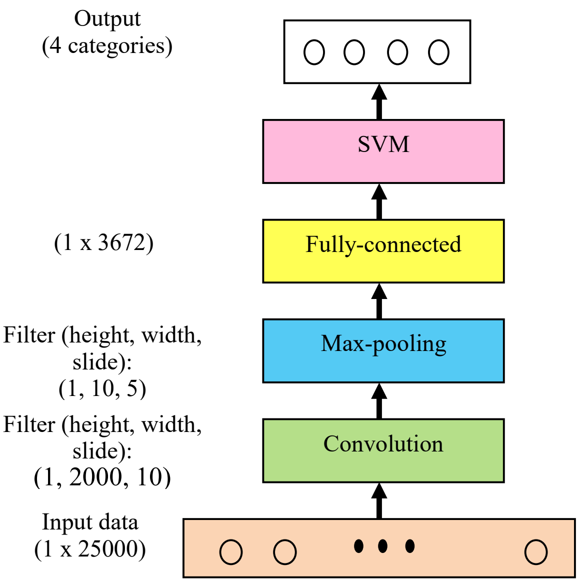


Figure 2. An architecture of a hybrid model composed by CNN with SVM[13]

3.3. A hybrid model composed by CNN and SVM

The hybrid mode[13] composed by convolutional neural network (CNN) and SVM is shown in **Figure 2**. SVM is adopted instead of the top fully connected layer in the conventional CNN. The parameter modification is performed separately, i.e., CNN in **Figure 1** is pre-trained by BP method, and then SVM, which is adopted to the CNN deleting the final full connection layer as shown in **Figure 2**, is trained by its supervised learning method.

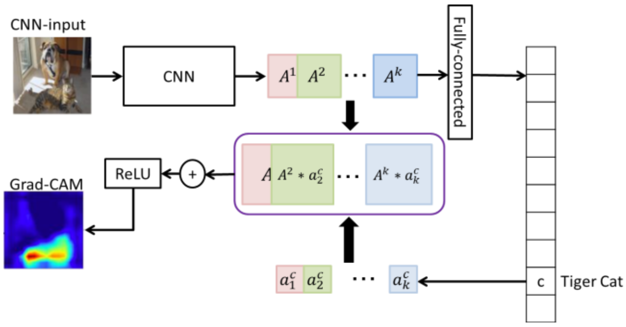


Figure 3. An architecture of Grad-CAM[6] used in this study.

3.4. Grad-CAM

To show how a deep convolutional neural network (CNN) works well in pattern recognition, Selvaraju *et al.* proposed an approach – Gradient-weighted Class Activation Mapping (Grad-CAM) [6]. By visualizing the difference between connection weights of full-connected layers of CNN, Grad-CAM highlights the important region in the image for predicting the object which is recognized by CNN. Grad-CAM provides an interesting method for the Explainable Artificial Intelligence (XAI). In this study, Grad-CAM is adopted to analyze the characteristics of neural signals concerned with different episode memories. The processing flowchart of Grad-CAM is shown in **Figure 3**. An image and a class of interest (e.g. "tiger cat" or "dog" in the image) are input to a CNN with fully connected layers, and the CNN outputs the probability of the class, then the features (connection weights to fully connected layers) $A^1, A^2, ..., A^k$ are set to zero for all classes except the interest class ("tiger cat"), which is set to 1.0 by an one-hot vector coefficient $a_1^c, a_2^c, ..., a_k^c$. The modified features are represented by an image of heatmap according to a ReLU active function, and the area of the interest class is visualized. The details of the Grad-CAM are in Ref. 6.

In this study, Grad-CAM is utilized to find the relationship between the patterns of MUA signal and different episodic memories. In other words, by observing the change of brain waves, we can estimate what kind of memories of events, experiences of animals are consolidated or associated in the brain (hippocampus), and vice versa.

4. Experiments and Results

4.1. Neural signals and events for episodic memories

The data of MUA used in this study were provided by Ishikawa, Tomokage, and Mitsushima[5]. Vertically movable

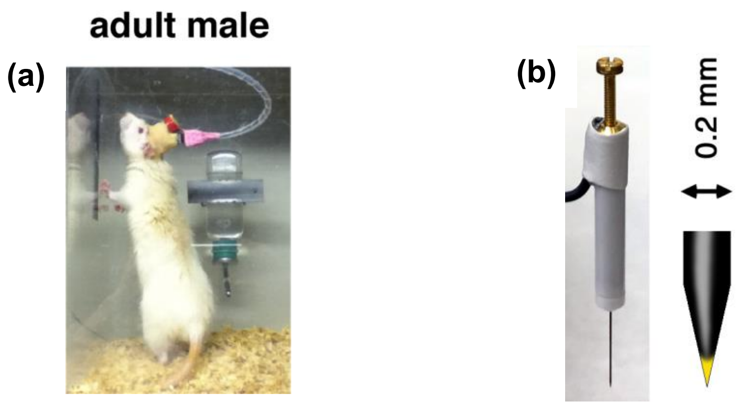


Figure 4. *In vivo* recording of MUA of a rat[5]

(a) An adult male rat implanted with an electrode (b) Electrode used for recording

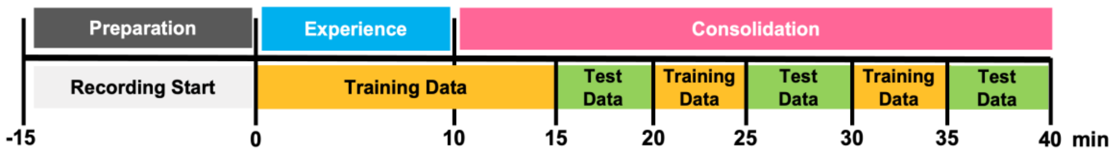


Figure 5. Schedule of MUA recording[5] and the data used in event recognition experiment.

recording electrodes (Unique Medical Co., LTD, Japan) were implanted above the hippocampal CA1 (posterior, 3.0 - 3.6 mm; lateral, 1.4 - 2.6 mm; ventral, 2.0 - 2.2 mm) of rats at the age of 15 to 25 weeks (**Figure 4**). Rats were housed individually and excluded if electrodes did not target the region of neurons. MUA, *in vivo* recorded time series data of multi-unit activity of CA1, were band-pass filtered at 300 - 10k Hz, and mostly sampled at 25k Hz.

The recording schedule is shown in **Figure 5**. In **Figure 5**, “Preparation” indicates the period after the recording of basal condition (at least 15 min); “Experience” indicates the four kinds of candidate events given to the rats –restraint stress, a first encounter with a female, male, and novel object, i.e., a yellow LEGO®/DUPLO® brick (10 min); “Consolidation” indicates the period after events when rats were return to their home cages (more than 30 min) (see **Table 1**.).

“Training Data” and “Test Data” in Figure 5 indicate the training samples for the modification of machine learning models (CNN with SVM), and unknown data for testing the performance of the models, respectively. Details of these data used in the episode memory recognition experiment are shown in **Table 2**. As the first challenge to the classification of MUA signals by the deep learning methods, one male rat’s data were used in the machine learning experiment and more male rats’ data were prepared by the MUA measurement experiments and they will be utilized in the ripple-wave recognition in the future.

Four kinds of events time series data of multiple-unit firing activity of CA1 neurons of the rat, is shown in **Figure 6** (Scale of horizontal axis: 1/25,000 sec).

4.2. Parameters of machine learning models

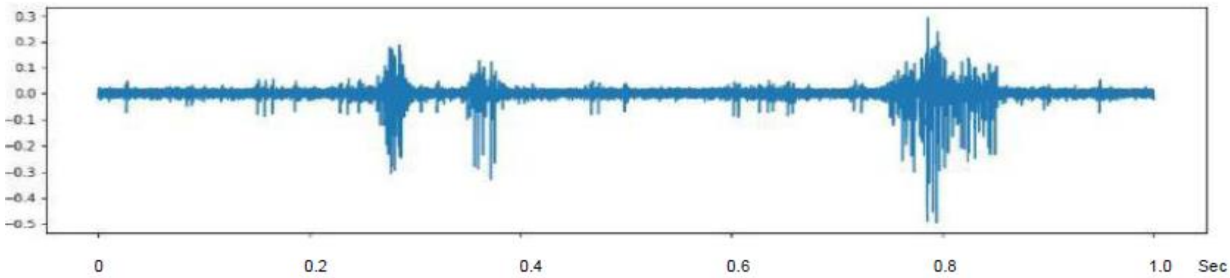
As shown in **Figure 1** and **Figure 2**, the time series data were used as same as an image data which had a size of $1\times 25,000$ (height x width) as the input to CNN. The size of convolution layer of CNN was $1\times 2,000\times 10$ (height x width x slide), and max-pooling $1\times 10\times 5$. The number of units in fully connected layers were 3,672, and 500, and the output was 4. The input to SVM in the case of **Figure 2** was 500, and the kernel function of SVM used Radial Basis Function (RBF).

Table 1. Events for rat’s episodic experiences in the experiment.

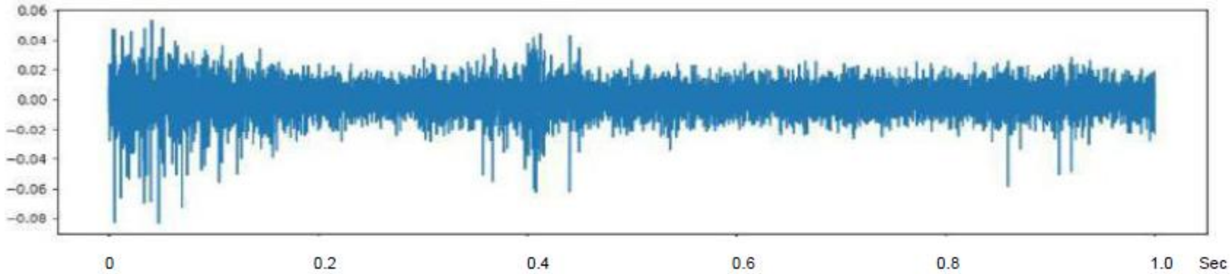
Event	Contents
restraint	Restraint stress
object	Contact with a novel object
female	Contact with a female
male	Contact with a male

Table 2. Data used in pattern recognition experiment.

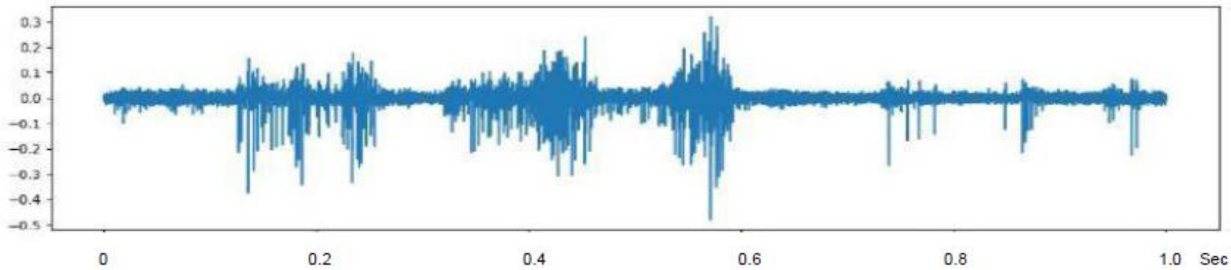
Name	Value
Sampling rate	25k Hz
Input of CNN (dimensionality)	25,000
The number of training data	1,500/event, 4 events (classes)
The number of test data	900/event, 4 events (classes)



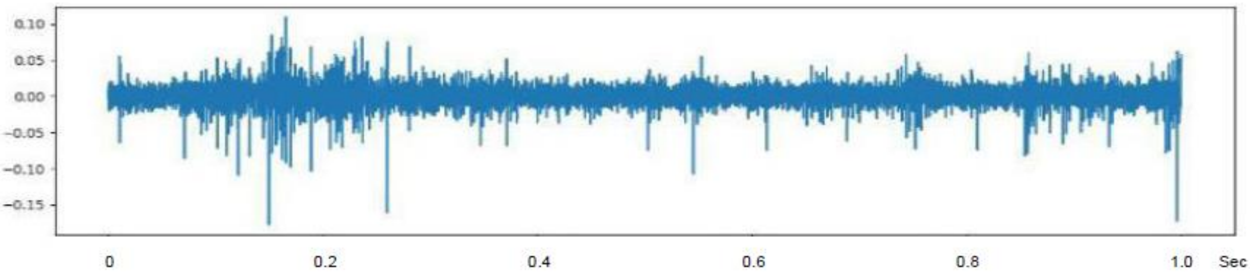
(a) Restraint



(b) Female



(c) Male



(d) Object

Figure 6. The time series data of MUA used in episodic memory recognition experiment.

4.3. Episode memory recognition results

The recognition accuracies of 4 kinds of episodic memories (shown in **Table 1**) were 50.0%, 85.3%, and 89.4% by the machine learning methods SVM, CNN[11], and CNN with SVM[11], respectively. Detail accuracies of different events by CNN and CNN with SVM were compared in **Figure 7**. It can be confirmed that the events of "Female" (The adult male rat met a female rat firstly), "Object" (The rate met a novel object, i.e., a brick of LEGO®), had higher values comparing to other events ("Male" and "Restraint").

Confusion matrixes of the recognition results of CNN and CNN with SVM are shown in **Table 3** and **Table 4**.

Precisions (=TP / (TP+FP)), Sensitivities (= TP / (TP + FN)), and F-measures (= 2 * Precision * Sensitivity / (Precision + Sensitivity)) are calculated by the confusion matrixes and shown in **Table 5** (average values of 4 classes). It can be confirmed that the hybrid deep learning method CNN with SVM[13] had higher recognition accuracy than the shallow CNN[11].

Table 3. Recognition results by CNN[11].

	Precision	Sensitivity	Accuracy	F-measure
CNN	0.8593	0.8525	0.8525	0.8559
CNN with SVM	0.8952	0.8942	0.8942	0.8942

Table 4. Recognition results by CNN with SVM[13].

		True Class				Total
		restr.	**male**	**female**	**object**	
CNN	**restr.**	570	124	12	2	708
	male	330	776	0	1	1107
	female	0	0	867	41	908
	object	0	0	21	856	877
	Total	900	900	900	900	3600

Table 5. Comparison of recognition results given by different deep learning methods.

		True Class				Total
		restr.	**male**	**female**	**object**	
CNN with SVM	**restr.**	708	122	10	1	841
	male	192	772	0	1	965
	female	0	0	862	21	833
	object	0	6	28	877	911
	Total	900	900	900	900	3600

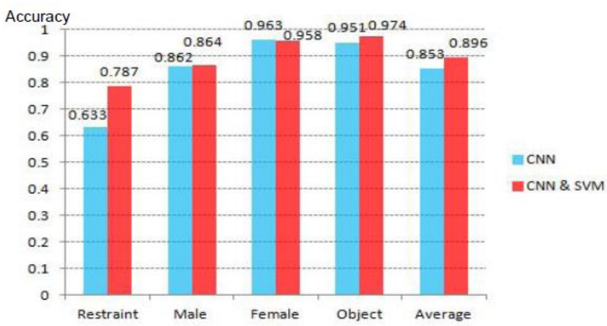


Figure 7. The recognition accuracies of different events by CNN and CNN with SVM.

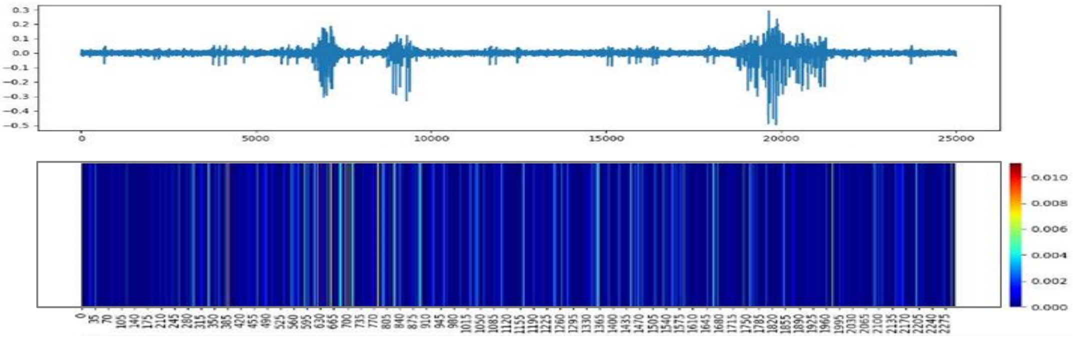
4.4. Analysis of relationship between MUA signals and memories by Grad-CAM and PCA

The experiment results reported in Section 4.3 suggest that the deep learning models can recognize the episodic memorization activities of hippocampus according to the input MUA signals. Meanwhile, it is interesting to find the pattern of MUA signals corresponding to the different memory activities, i.e., by observing the change of MUA signals, episodic memory activities occurring in the brain can be estimated. Using Grad-CAM described in Section 3.4 and the succeed results of recognition by CNN with SVM, heatmaps of related patterns of MUA signals are obtained and samples of them are shown in **Figure 8**. Note the number of input time series data of MUA signal for CNN was 25,000 (1sec, 25kHz), the slide number of convolutional filter of CNN was 10 (for 5,000 data), so the number of features was 2,500 (horizontal axis in blue heatmap in **Figure 8**).

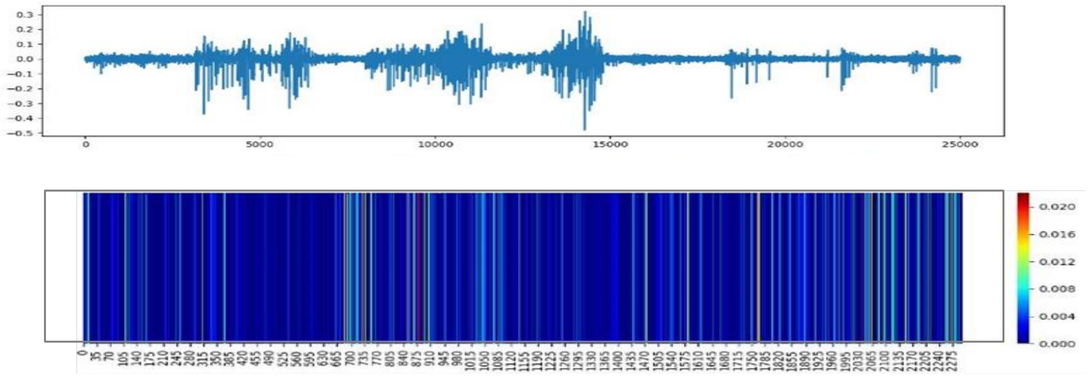
By choosing the highest value of heatmap given by Grad-CAM, the specified pattern of MUA signal related to the different episodic memories were masked, and these event-related signals are shown in **Figure 9**. To analysis the difference of these signals, principal component analysis (PCA), Fourier transform, and Cepstrum analysis were adopted. To describe the feature of original signals (time series data), Fourier transform shows the composition of different frequencies and Cepstrum transform, which is an inverse Fourier transform of the logarithm of signal spectrum given by Fourier transform, is able to show the periodic structures in frequency spectra. The Fourier and Cepstrum transform results are shown in **Figure 10** and **Figure 11**, respectively. It is difficult to confirm the difference of these transformed data, so the distributions of principle components of the power spectrum and Cepstrum given by PCA are shown in **Figure 12**. As shown in **Figure 12** (a), the classes of 4 events are not separated by the first and second components of Fourier transform data, however, they are categorized by Cepstrum transform as shown in **Figure 12** (b). The pattern of "object" closes to the case of "female", meanwhile, "restraint" and "male" almost overlapped

4. Conclusion

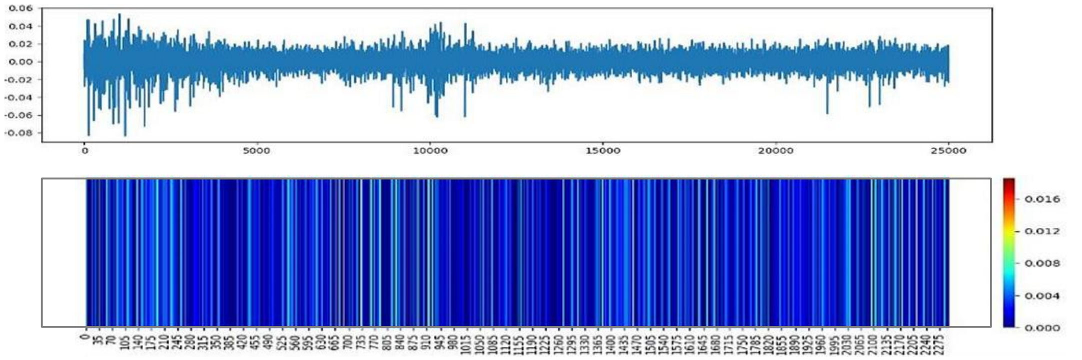
To recognize the episodic memory activities in hippocampus, machine learning methods such as support vector machine (SVM), convolutional neural networks (CNN), and a hybrid model composed by CNN and SVM were utilized and compared in this study. Using the time series data which were multi-unit activity (MUA) of CA1 in hippocampus corresponding to 4 kinds of experience events of an adult male rat, episodic memory recognition experiment results showed the priority of the hybrid classifier CNN with SVM which recognition accuracy was 89.42%, meanwhile accuracies of a single CNN and a single SVM were 85.25%, and 50.0%, respectively. Additionally, the relationship between the pattern of MUA and episodic memories was investigated by the visualization of the heatmap of CNN features using Grad-CAM. According to the investigation results, characteristic MUA were extracted, and they were successfully classified by PCA with cepstrum transform data. The future work of this study may be the additional recognition experiment using more data collected by more rats and events to discover the specified MUA concerning to the episodic memory activities in hippocampus.



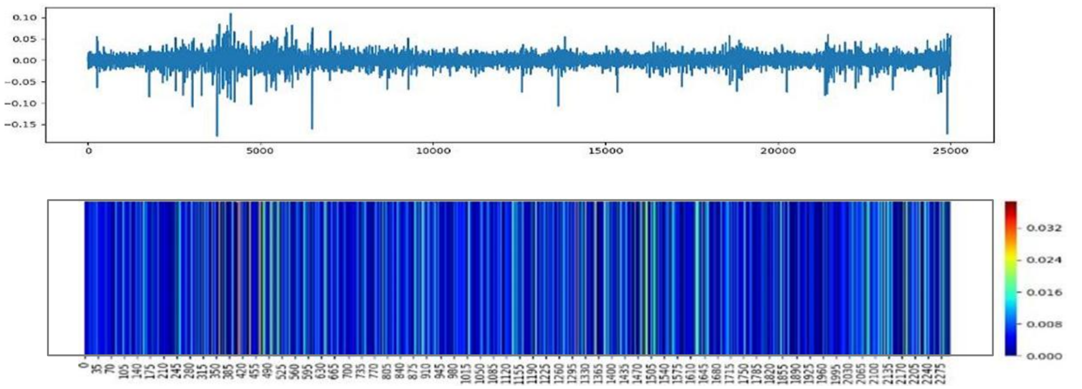
(a) Restraint



(b) Male

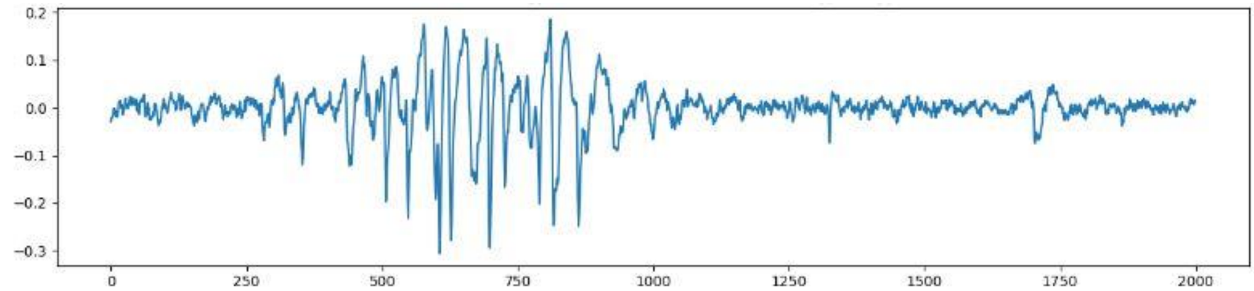


(c) Female

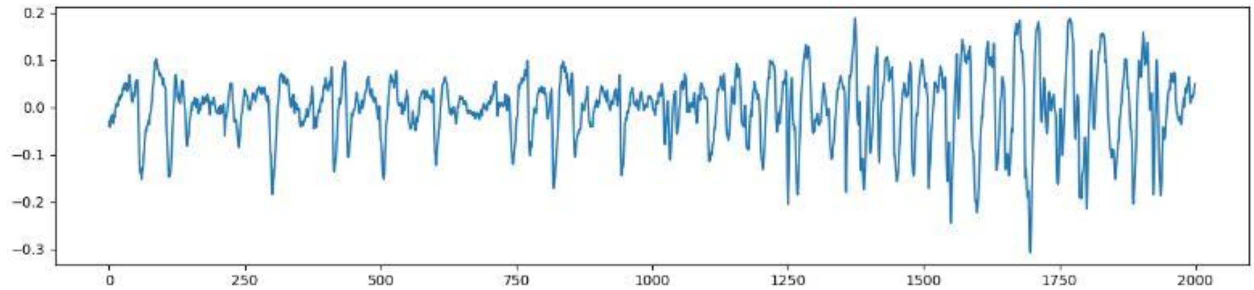


(d) Object

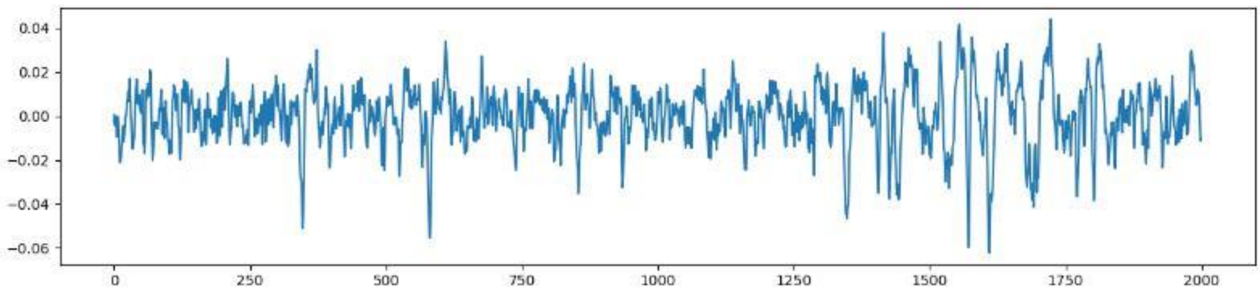
Figure 8. MUA signal and their heatmap of the event concerned features in CNN (horizontal axis in blue heatmap: feature number).



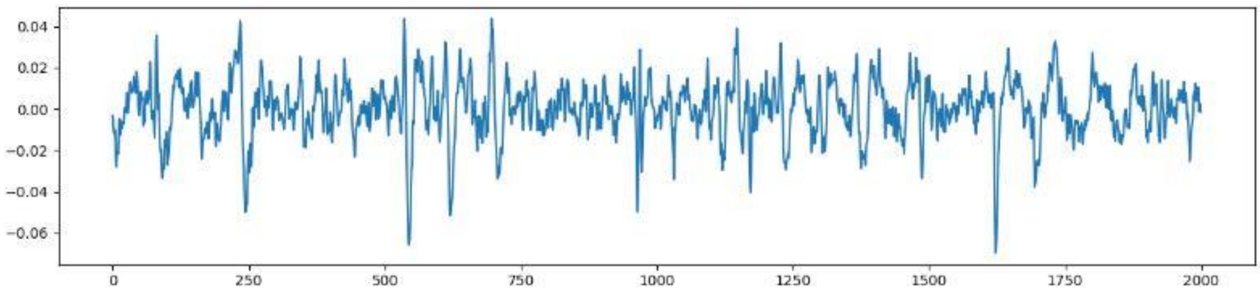
(a) Restraint



(b) Male

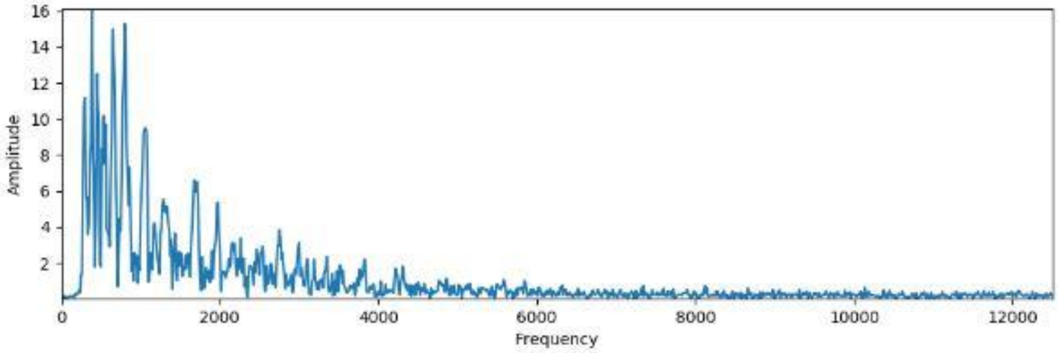


(c) Female

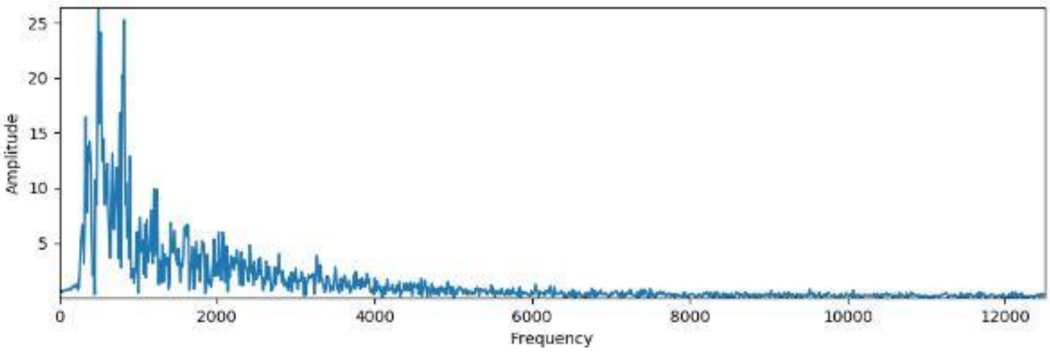


(d) Object

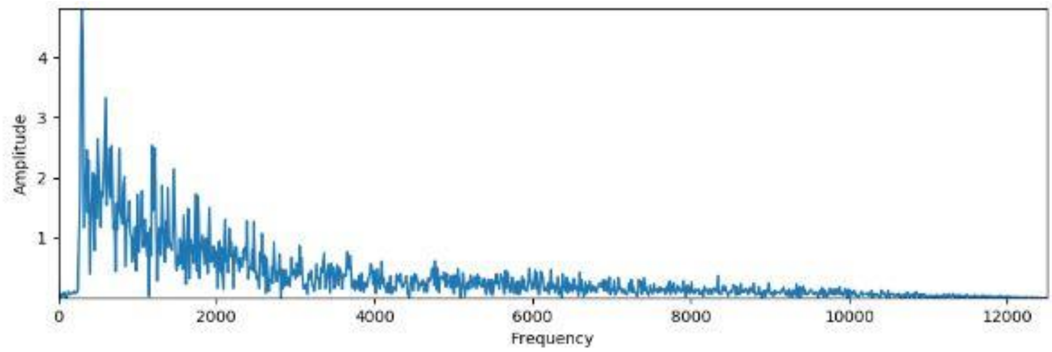
Figure 9. Specified pattern of MUA signal related to the different episodic memories (Scale of horizontal axis: 1/25,000 sec).



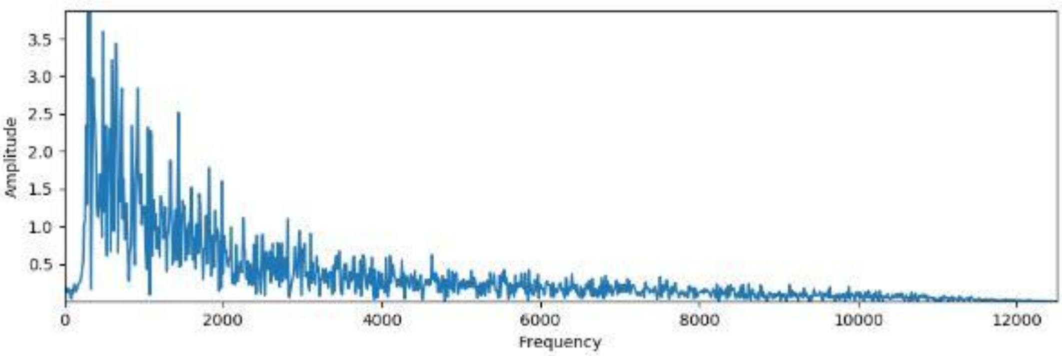
(a) Restraint



(b) Male

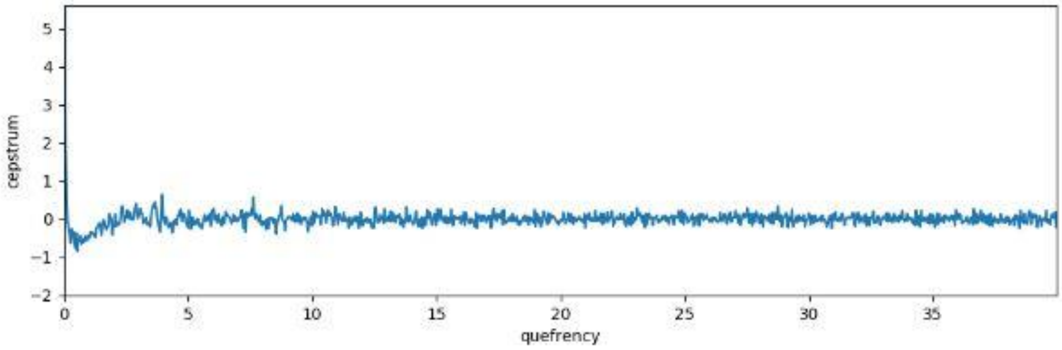


(c) Female

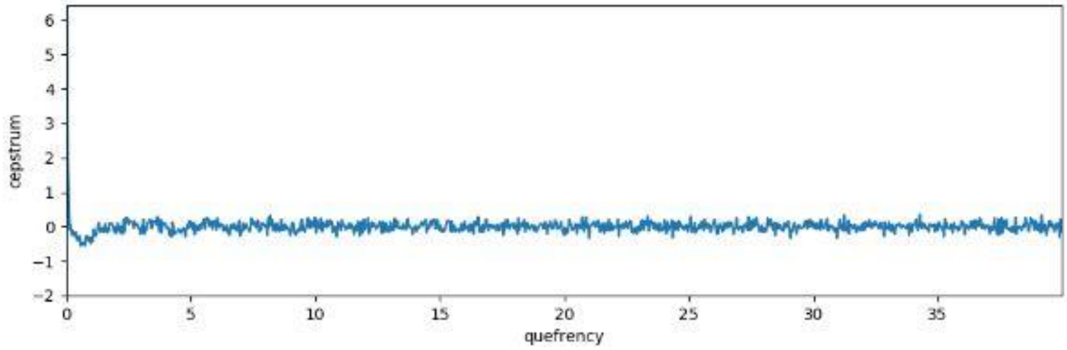


(d) Object

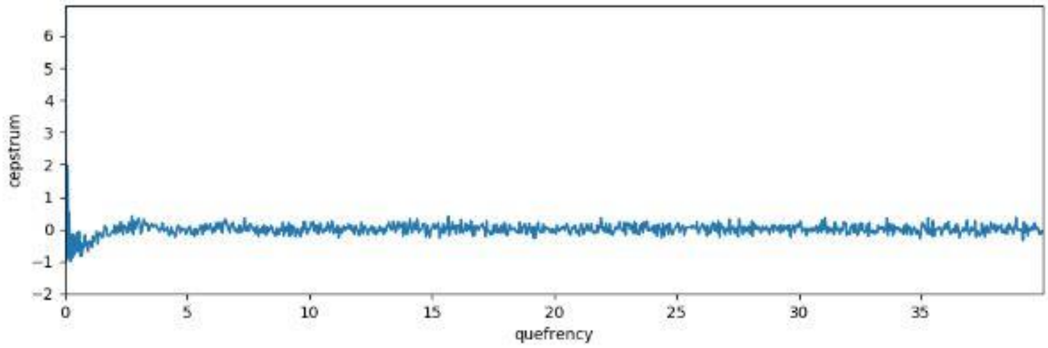
Figure 10. Fourier transform result of the specified intervals of MUA extracted by Grad-CAM (Scale of horizontal axis: Hz).



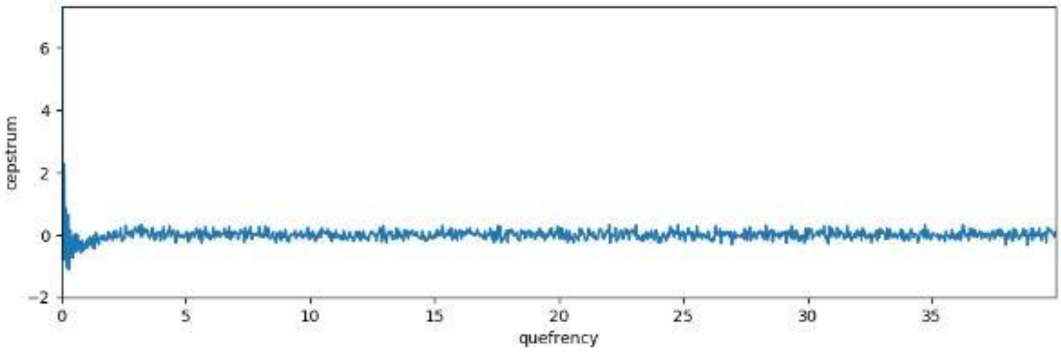
(a) Restraint



(b) Male

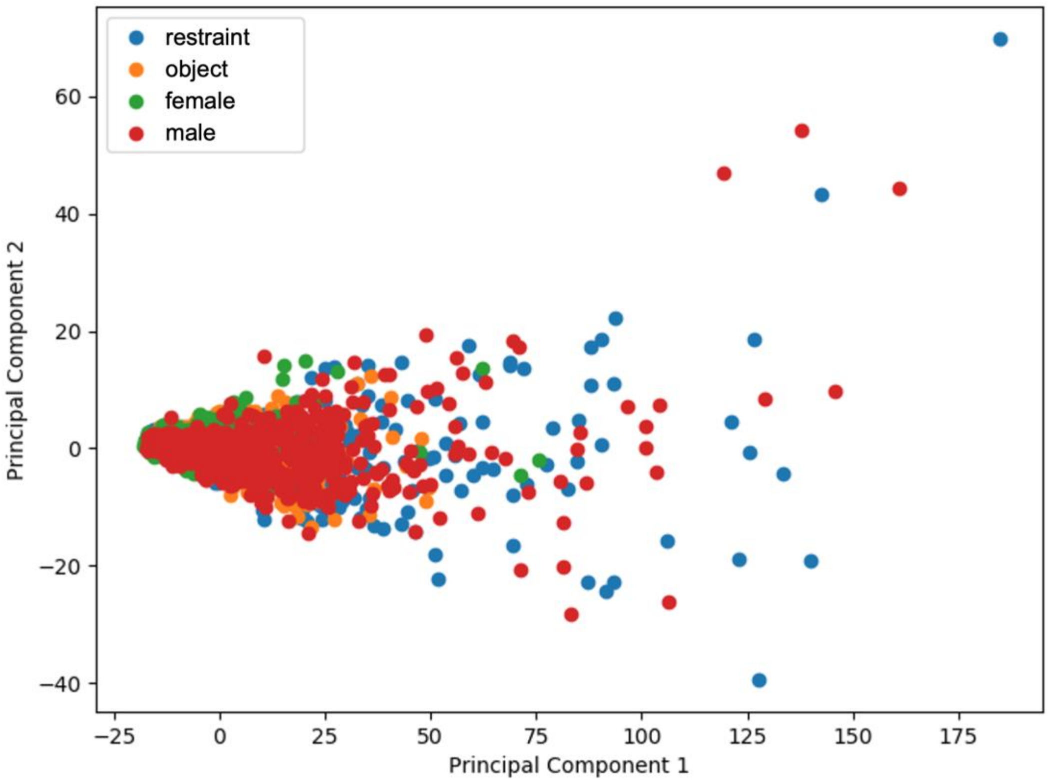


(c) Female

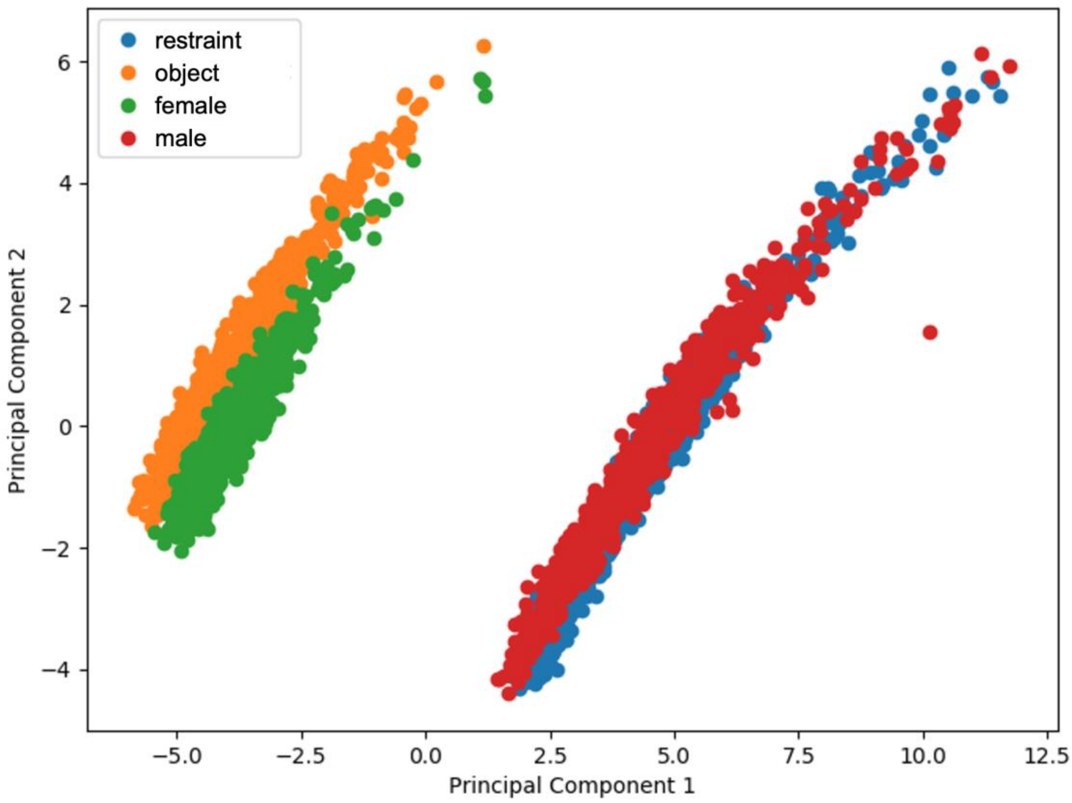


(e) Object

Figure 11. Cepstrum transform results of the important intervals of MUA signals extracted by Grad-CAM (Scale of horizontal axis: msec).



(a) The case of Fourier transform



(b) The case of Cepstrum transform

Figure 12. Classification result by PCA for different patterns of MUA.

Conflict of interest

The authors declare no conflicts of interest.

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