ABSTRACT—Kratom (KT) typically exerts antidepressant (AD) effects. However, evaluating which form of KT extracts possesses AD properties similar to the standard AD fluoxetine (flu) remained challenging. Here, we adopted an autoencoder (AE)-based anomaly detector called ANet to measure the similarity of mice’s local field potential (LFP) features that responded to KT leave extracts and AD flu. The features that responded to KT syrup had the highest similarity to those that responded to the AD flu at 87.11 ± 0.25%. This finding presents the higher feasibility of using KT syrup as an alternative substance for depressant therapy than KT alkaloids and KT aqueous, which are the other candidates in this study. Apart from the similarity measurement, we utilized ANet as a multi-task AE and evaluated the performance in discriminating multi-class LFP responses corresponding to the effect of different KT extracts and AD flu simultaneously. Furthermore, we visualized learned latent features among LFP responses qualitatively and quantitatively as t-SNE projection and maximum mean discrepancy distance, respectively. The classification results reported the accuracy and F1-score of 90.11 ± 0.11% and 90.08 ± 0.00%. In summary, the outcomes of this research might help therapeutic design devices for an alternative substance profile evaluation, such as Kratom-based form, in real-world applications.

Index Terms—Anomaly detection, antidepressant, kratom, local field potential, multi-task autoencoder.

I. INTRODUCTION

KRATOM is a local name of Mitragyna speciosa (Korth.) Havil. and has been broadly recognized as herbal medicine for many decades. It can effectively treat and improve withdrawal symptoms and psychological disorders induced by abuse drugs in both animal models [1], [2], [3], [4], and human [5], [6]. KT leaves extract and its major alkaloid constituent, mitragynine (MT), have been reported to have antidepressant (AD)-like activity on the central nervous system (CNS) [1], [7], [8], [9]. So far, although AD effects of KT leave extract have apparently been documented, KT leaves extracts have been deployed in pre-clinical and clinical scales in many forms, such as KT aqueous extract (KTaq), alkaloid (Ktalk) extract and KT syrup (Ktsyr) [1], [2], [3], [9], [10]. As a result, it was still unclear which kind of KT leaf extract might have a profile similar to standard AD.

Local field potential (LFP) recording is an invasive measurement to capture brain working, providing high temporal resolution and sensitivity. The spectral power of LFP oscillates dependently on the alteration of the neuro-biomolecules (NeuroBios) and is a conventional method in drug profile classification in rodents [11]. However, manually analyzing with the
conventional method when there are a large number of drugs to be identified is impractical and time-consuming, especially when each drug has similar effects on LFP features. Therefore, the machine learning approach is an alternative way for users to recognize LFP features in higher complexity tasks [12]. There are a few works that attempted to extract essential LFP features from animals with the deep neural network on classification applications [13], [14]. However, a study focusing on drug similarity analysis applications is still lacking. Therefore, we desire to propose a novel neural network pipeline for measuring the similarity of LFP response to substances in mice.

A compressed sensing method, autoencoder (AE), is a computational-based deep learning architecture or model [15], [16], [17]. AE primarily consists of two components: an encoder and a decoder. The encoder’s main function is to map the input signals to latent space; meanwhile, the decoder’s function is to reconstruct the latent vector to be the input signals [18]. Later, Ditthapron et al. proposed multi-task AE, which integrated a supervised classifier network into the AE. This improves the AE data compression and reconstruction capability while simultaneously classifying the brain signals [19]. In terms of application, although tiny alteration of the brain working in a fraction of a millisecond, such as during performing imaginary motor tasks as well as examining the test to diagnose developmental dyslexia, which is generally difficult to distinguish by visual inspection, the multi-task AE can classify well by having the raw EEG signal as the inputs of the models [20], [21]. As far as we know, one study utilizes the multi-task AE for LFP signals [22]. However, they focus on the dimensionality reduction of neural features without further application. Thus the study related to mice’s LFP response to given substances and the substances similarity analysis application, as in the rest of the paper, is a novel issue.

Here, we proposed the AE-based anomaly detector called ANet as the LFP feature extractor that can measure the similarity of mice’s LFP administering KT extracts and AD fluoxetine (flu). Fig. 1 demonstrates an overview of the pipeline for ANet utilization, while Fig. 2 illustrates ANet and extended ANet (multi-task AE, which is AE and supervised learning) architecture.

- ANet is an anomaly detector that can automatically extract essential features, which is proven through the latent space qualitatively and quantitatively as t-distributed stochastic neighbor embedding t-SNE projection and maximum mean discrepancy (MMD) distance, respectively. Utilizing these features, ANet can assess the similarity between two LFP induced by different types of substances. With an extension of the supervised learning component, extended ANet can be used to classify LFP response induced by the multiple KT extracts and AD flu.

- Based on mice’s brain responses or LFP evaluated using ANet and the extended ANet, we found that KT syrup produced the highest similar LFP features to AD flu. To the best of our knowledge, we are the first to reveal that using KT syrup extract is an appropriate candidate substance for depressant therapy. However, further confirmation of the clinical study on AD effects from KT syrup remains a future challenge.

II. MATERIALS AND DATA GATHERING

A. Kratom Leave Extracts

We collected KT leave from the natural resources in Surat Thani province, Thailand. Supplementary materials explain
more details about the preparation of KT extract and the quantification of KT major alkaloids, mitragynine (MT), that accumulated in each form of KT extracts.

B. Mice

The committee approved all operations involving animals employed in the scientific study from the Prince of Songkla University’s Institute of Animal Care and Use, which followed the criteria of the International Committee on Laboratory Animal Science (ICLAS) [project license number: MHESI 6800.11/845 and reference number: 57/2019]. We recruited 35 Male Swiss albino ICR mice from the Nomura Siam International Company, Bangkok, Thailand. They were appropriately at rest for one week before the experiment began to minimize the stress. Moreover, mice stayed in separated stainless steel cages (17 × 28.5 × 17 cm) under the standard condition room (12/12 h light/dark cycle, 22°C, and 55.1% relative humidity). Water and commercial food pellets were accessed freely. We conducted the studies between 8 AM and 4 PM. There were five treatment groups in this experiment, and seven mice were used per group.

C. LFP Electrode Implantation

Male ICR mice (four months of age) had been through an intraperitoneal injection of a mixed solution of 16 mg/kg xylazine hydrochloride (Xylavet, Sigma-Aldrich International GmbH, Switzerland) and 50 mg/kg zoletil (Tiletamine – zolazepam, Vibac Ah, Inc., USA) to be deeply anesthetized. The head of the animals was then fixed with stereotaxic apparatus before the scalp on the dorsal head in the middle line was exposed. According to the mouse brain atlas [23], electrodes were stereotaxically implanted on the left hemisphere of the brain, from the bregma to the medial prefrontal cortex (mPFC) (AP; +2.5 mm, ML; 0.2 mm; DV; 1.5 mm), hippocampus (HP) (AP; −2.5 mm, ML; 2.0 mm; DV; 1.5 mm) and the nucleus accumbens (NAc) (AP; +1.3 mm, ML; 1.0 mm; DV; 4.2 mm). Over the cerebellum (AP; −6.0 mm, ML; 0.0 mm; DV; 1.5 mm), a ground electrode was inserted. Dental acrylic was applied to hold and secure all placed electrodes. The antibiotic ampicillin (100 mg/kg) (General Drug House Co., Ltd., Bangkok, Thailand) and carprofen (10 mg/kg) (Best Equipment Center Co., Ltd., Thailand) were given intramuscularly once a day for three days [3], [24] to prevent infection and relieve pain. It took at least two weeks to fully recuperate from surgery before they could begin the experiment.

D. Data Collecting in Mice

As soon as animals recovered from surgery, they went to the experimental period adapted from the previous investigations [2], [11], as shown in supplementary materials. In brief, after animals habituated for three consecutive days, they went to the testing phase. During this phase, we placed mice individually in the recording chamber (25 cm × 18 cm × 25 cm) to familiarize the experimental conditions for one hour. After that, the LFP signals were harvested in the recording session for 30 minutes after the injection of the treated substances (number of mice = 7 per group) for one hour. According to the high-performance liquid chromatography examination, the concentrations of KT extract in each form could be found in Table 1. KT extract calculated doses are from the whole amount of sample containing MT, fixed at 10 mg/kg, a dose that effectively cured the animal model of depression [8]. The AD flu at 10 mg/kg was selected as the standard drug since it showed positive results in previous findings [1]. This whole experiment protocol for collecting LFP signal is illustrated in the supplementary document Figure S2.

Details of the instrumental setup for recording LFP signals can be found in our prior works [3], [25]. In summary, the Dual Bio Amp (AD Instruments, Castle Hill, NSW, Australia) and the PowerLab 16/35 system (AD Instruments, Castle Hill, NSW, Australia) with 16-bit A/D at a sampling frequency of 2 kHz are used for LFP signal amplification and digitization, respectively. The digitized signal was recorded, and the power line noise artifact of 50 Hz was filtered out using LabChart 7.3.7 Pro software.

III. EXPERIMENTS

This work has designed three experiment settings: Spectral Power with Statistical Analysis, AE-Based Anomaly Detection, and Multi-Task AE. The purpose and detail of each experiment are described below.

A. Experiment I: Spectral Power With Statistical Analysis

This experiment’s purpose was to compare LFP responses induced by different substances with the traditional method. The substances used are control, AD flu, KT syrup, KT alkaloids, or KT aqueous. First, we downsamled raw LFP to 200 Hz using the MNE python package (version 0.23.4) [26]. Then we computed the spectral power of the prepared LFP for all channels by applying the Morlet wavelets transform and divided into six frequency bands: Delta, Theta, Alpha, Beta, Gamma I, and Gamma II according to the previous works [24], [27]. Finally, we conducted the statistical analysis using a non-parametric Kruskal-Wallis test with Bonferroni multiple comparisons to test group differences across the frequency bands at each brain region.

Comparing statistical results to the deep learning approaches, the recorded LFP signals at each brain region were further split into four seconds per segment, followed by spectral power of the frequency band extraction. The processed signal is used as the input to ANet and the multi-task AE in the following two experiments, as shown in Figs. 3 and 4.

| Sample       | MT content (Mean ± SD) | Amount of MT per administration | Dose of each sample per administration |
|--------------|------------------------|----------------------------------|----------------------------------------|
| KT alkaloids | 47.10 ± 0.55 mg/g DW   | 10                               | 212 mg                                 |
| KT aqueous   | 10.80 ± 0.00 mg/g DW   | 10                               | 926 mg                                 |
| KT syrup     | 2.30 ± 0.00 mg/mL      | 10                               | 4.35 mL                                |

Note: DW designated as dry weight. The samples were analyzed in triplicate.
Fig. 3. The procedure of Experiment II: AE-Based Anomaly Detection (ANet)
Note: Number of frequency bands ($F$), Number of brain areas ($B$), Number of time points ($T$), the LFP features in response to each substance: KT syrup (KT-syr), KT aqueous (KTaqu), KT alkaloids (KTalk), and antidepressant fluoxetine (AD flu).

B. Experiment II: AE-Based Anomaly Detection (ANet)

This experiment aimed to evaluate the similarity of LFP features responded to each KT extract relative to the reference drug (AD flu). We first designed the structure of the autoencoder or ANet as shown in Fig. 2. Notes that the detail parameters of the architecture are demonstrated in the supplementary document Table S1.

1) Encoder: The encoder network contained two convolutional neural networks (CNN) stacks; each consisted of a 2-D convolutional layer (Conv2D) performed with a rectified linear unit (ReLU) activation function, a batch normalization layer, and an averaging pooling layer (AveragePooling2D), respectively. Notes that ReLU activation function was chosen after to optimize the results from our architecture as shown in the supplementary document Table S2 to S4. In this module, the input format was ($F \times B \times T$), where $F$, $B$, and $T$ denote the number of frequency bands, brain areas, and time points, respectively. During the implementation, we set a data format as the channel last option for Conv2D (Keras API). Flatten was the final layer before mapping to the latent representation or vector.

2) Decoder: The decoder aligned symmetrically with the encoder component to shape the dimension of reconstructed signals to be the exact size of the original input. Three CNN blocks reconstruct the information from the latent vector. Each CNN block of the decoder network consisted of a Conv2D activated by the ReLU function, followed by a UpSampling2D layer to expand the spatial dimension of the data.

To build ANet to be the anomaly detector, as illustrated in Fig. 3, LFP spectral power responded to AD flu was the original input during training as the conventional AE. We calculated and used mean square error (MSE) loss (2) to optimize ANet during the training phase according to the following Subsections III-D and III-E. After the final iteration of training, the mean and standard deviation (SD) of MSE loss is used to define the threshold for the normal zone of the anomaly detector. The width of the normal zone was the mean $\pm$ SD. Then we used the trained ANet to evaluate the similarity of the unseen LFP features that responded to KT extracts (testing sets). If MSE loss of the unseen LFP fell into the normal zone, LFP features that responded to the KT extract are deemed similar to standard AD drugs and vice versa.

C. Experiment III: Multi-Task AE

This study extended ANet by including the supervised learning component to the AE, which turned out to be the multi-task AE. We aimed to perform the feasibility of extracting discriminative features from multiple LFP responses simultaneously.

ANet and Supervised Learning: We added the supervised learning component by having the latent vector layer of ANet as the input, which made the proposed architecture form the multi-task AE, as shown in Fig. 2. At the end of the supervised task, the softmax function classified the latent vector via layer activation in the FC layer. These allowed our model to learn the reconstruction along with the classification.

During the experiment, we explored the possibility of the multi-task AE or the model recognizing the multi-class LFP features for classifying LFP responses. We believed that this experiment could benefit in developing computational tools for future studies of the substance that affected mice’s brain activities. The experimental protocol followed Fig. 4. Firstly, we split the inputs for training, validating, and testing sets. Then we optimized the model according to the following Sections III-D and III-E. Eventually, the following bullets and equation explain quantitative and qualitative assessments of the model capability in LFP feature extraction.

- $t$-SNE projection is for the qualitative assessment of the visualize reduced dimensional data [28]. In this experiment, we defined the latent vector as the input of $t$-SNE projection algorithm to present the probability distribution
of unlearned and learned features, representing the LFP datasets before and after feature extraction by the proposed model, respectively.

- **Maximum Mean Discrepancy (MMD) distance** is for the quantitative assessment of the distance between the means of the embedding features of two probability distributions in t-SNE projection. They evaluated whether data in set $X$ and $Y$ generated a probability distribution equally. Here, the ideal concept is that if the MMD distance of LFP features between substance $X$ and $Y$ is low. Then, we might imply that those two LFP inputs seem to originate from a very close origination. Assuming that we have probability distribution of LFP; $P_X$ and $P_Y$ over set $\chi$. The standard calculation of MMD can be expressed by (1).

$$MMD(P_X, P_Y) = \|E_{X\sim P_X}[\varphi(X)] - E_{Y\sim P_Y}[\varphi(Y)]\|_\kappa$$

(1)

Where $\kappa$ denotes a reproducing kernel Hilbert space and $\varphi$ represents the map of feature $\chi$ to $\kappa$. $E_{X\sim P_X}[\varphi(X)]$ refers to expected random $X$ value after mapping to $\kappa$ from distribution $P_X$. Notes that we used the Gaussian kernel for feature map $\varphi$ in this work. In addition, the multi-task AE performance also exhibited averaged percentage accuracy, F1-score, and confusion matrix.

D. Network Training

In both Experiment II and III, we implemented our model using Keras API (TensorFlow version 2.2.0 as backend) under NVIDIA Tesla v100 GPU setup with 32 G memory. We use the Adam optimizer and the learning rate decay algorithm with a start learning rate of $10^{-4}$. If the validation loss did not improve for five consecutive epochs, the learning rate gradually declined with a decay rate of 0.5 until the learning rate reached $10^{-5}$. The batch size was 128 samples. We applied the function of early stopping to stop the training iteration when the validation loss had not reduced for 20 continuous epochs. We utilized the model’s weight which provided the lowest total loss in the testing phase.

According to the described experiments earlier, we optimized mean square error (MSE) loss alone for Experiment II or the study of ANet. In contrast, we optimized both MSE and cross-entropy (CE) losses for Experiment III, which studied the multi-task AE. ANet and the supervised learning components were simultaneously trained and optimized without freezing any layers. MSE and CE losses correspond to AE and supervised learning components, respectively, as described below:

- Mean square error (MSE) loss was adopted to monitor and minimize errors between the input signal and reconstructed data. It was expressed in (2).

$$L_{MSE}(x, \hat{x}) = \frac{1}{C} \sum_{i=1}^{C} \|x_i - \hat{x}_i\|^2$$

(2)

$C$ represents a number of channels while $x$ and $\hat{x}$ are input and reconstructed data of the channel.

- Cross-entropy (CE) loss was used in supervised learning to assess the error between the actual label and classification probability, as shown in (3).

$$L_{CE}(y, \hat{y}) = -\sum_{j=1}^{c} y_j \log \hat{y}_j$$

(3)

Where $y_j$ and $\hat{y}_j$ denote true and predicted labels of data in class, and $c$ is the number of classes.

The summation of the losses, as mentioned earlier, finally evaluated the total loss: $L_{MSE}$ and $L_{CE}$ demonstrated in (2) and (3), respectively, as shown below.

$$L_{total}(x, \hat{x}, y, \hat{y}) = \frac{1}{N} \sum_{k=1}^{N} \left(L_{MSE}(x_k, \hat{x}_k) + L_{CE}(y_k, \hat{y}_k)\right)$$

(4)

$N$ is the total number of input signals and the weight of loss assigned for 1.0.

E. Network Validation

Experiment II validated ANet for anomaly detection with the subject-independent scheme. The stratified 5-folds cross-validation was adopted to separate data for testing, and training sets, both outer and inner loops, using StratifiedKFold() function from Scikit-Learn (version 1.1.1) [29]. Only the spectral power of LFP that responded to the AD flu was assigned as training and validation sets, while unseen data from KT extracts were used as a testing set, as illustrated in Fig. 3. The multiple LFP responses classification required a larger scale of samples in the network training, so Experiment III validated the multi-task AE with the subject-dependent scheme. The spectral powers of multi-LFP classes responded to each substance: control, AD flu, KT syrup, KT alkaloids, and KT aqueous gathered from seven mice per class, as shown in Fig. 4.

IV. RESULTS

A. Experiment I: Spectral Power With Statistical Analysis

The conventional LFP analysis method is to use statistical analysis on the hand-crafted spectral power features. This experiment used statistical testing across the quantitative spectral power analysis to assess the significant difference in LFP responses among the group of mice treated with different substances. As reported in Table II, the results found that LFP responses to KT syrup and KT alkaloids have no significant difference from AD flu in most brain regions and oscillation bands. In summary, the results convinced both KT extracts could be potential candidates for alternative drugs given the similar effects on the brain to AD flu. However, this conventional approach demonstrated the weakness in differentiating LFP responses from KT syrup and KT alkaloids. Thus, we addressed the weakness by proposing ANet and the multi-task AE approaches in identifying the higher similarity of LFP responses to KT syrup and AD flu compared to those to KT alkaloids.
TABLE II
SUMMARY OF PAIRWISE MULTIPLE COMPARISON TEST OF SPECTRAL POWER IN SELECTED PAIRED SUBSTANCES

| Brain region | Bands | Paired groups                  |
|--------------|-------|--------------------------------|
|              |       | AD flu vs. KT tyr vs. KT aque vs. KT alk | AD flu vs. KT tyr vs. AD flu vs. KT tyr vs. AD flu vs. KT alk |
|              |       | Delta                           | Theta | Alpha | Beta | Gamma I | Gamma II |
| Delta        |       | *                               | *     | *     | *    | *       | *        |
| Theta        |       | *                               | *     | *     | *    | *       | *        |
| Alpha        |       | *                               | *     | *     | *    | *       | *        |
| Beta         |       | *                               | *     | *     | *    | *       | *        |
| Gamma I      |       | *                               | *     | *     | *    | *       | *        |
| Gamma II     |       | *                               | *     | *     | *    | *       | *        |

Note: *, **, and *** represent $p < 0.05, 0.01, 0.001$, respectively.

Fig. 5. Histograms on anomaly tests were exhibited. The distribution of MSE loss from LFP features responded to the AD flu was illustrated along with each loss distribution of KT syrup (a), KT alkaloids (b), KT aqueous (c), and all forms of KT extracts (d). The lower and upper thresholds were specified for training loss from 0.015 to 0.028, labeled with black and red dash lines on each graph. Any samples dropped between these thresholds were indicated as similar to the LFP of the AD flu.

B. Experiment II: AE-Based Anomaly Detection (ANet)

Experiment II demonstrated the performance of the proposed anomaly detector or ANet in assessing the similarity of the unseen LFP compared to the AD flu which is the standard antidepressant substance in producing the drugs. The findings revealed the number of LFP that responded to KT syrup appeared to distribute mainly in the normal zone. This indicates the high similarity of KT syrup to the standard drug or AD flu. From Fig. 5(a), it is demonstrated that the distribution of KT alkaloids is inside the normal zone than the distribution of KT aqueous. Quantitatively, the normal detecting rate, or defined as the similarity rate in this study, was 87.11 ± 0.25%, 79.45 ± 0.35%, and 41.43 ± 0.31% when comparing the LFP response of AD flu to the responses from KT syrup, KT alkaloids, and KT aqueous extract, respectively.

C. Experiment III: Multi-Task AE

To investigate an insightful optimization process of the multi-task AE, we assessed the alterations of training and validation losses in the multi-LFP class recognition during the training process. Based on the least iteration stopped by early stopping, Fig. 6(a)–(c) demonstrated training and validation loss while training for 70 epochs for MSE loss, CE loss, and total loss, respectively. The findings demonstrated that MSE loss reached a relatively stable level after training for less than ten epochs. In addition, a gradual decrease in both the CE and the total losses can be seen during this training. Moreover, validation loss converged to the training loss, suggesting that the model training had not been overfitted, confirming this study’s well-trained model. All measures of the performance were applied together with the early stopping function. In summary, the proposed multi-task AE reached accuracy, and the F1-score of the model was 90.11 ± 0.11% and 90.08 ± 0.00%, respectively.

Furthermore, we also illustrated a confusion matrix of the predicted outputs. While the matrix revealed that almost all LFP samples that responded to the treated substances were primarily correctly classified, it was obvious that there were some misclassifications between the AD flu and KT syrup, as shown in Fig. 6(d). Thus, LFP samples from both classes might have similar spectral power features originating from sharing mechanisms exerted on the CNS and the brain. The finding was consistent with Sections IV-A and IV-B.

The 2-dimension of the t-SNE projection visualized the probability distribution of reduced dimensional data at latent space. It was found that t-SNE of baseline, processed from raw spectral power, diffused and mixed among classes of substances evenly to form one cluster, as shown in Fig. 7(a). Meanwhile, the characteristics of t-SNE resulting from the learned features or...
represented latent vectors appeared to be formed for correct clusters. For example, consistency with the experiments mentioned earlier and results, among KT extracts, the KT syrup cluster shared the intersect clusters of the AD flu mostly, as depicted in Fig. 7(b).

Although discriminative LFP features of KT extract distributed with the AD flu overlappingly in the $t$-SNE visualization, this result seems to provide only qualitative estimation. To get a concrete explanation, MMD distance, a value estimated from the $t$-SNE projection-based-latent vector evaluation, was thus analyzed quantitatively. The results exposed that LFP features of KT syrup was the first group showing the shortest MMD distance connected to control mice and was followed by the AD flu, KT alkaloids and KT aqueous, respectively. Moreover, features in LFP responses from the AD flu:KT syrup was the first paired class that produced the shortest MMD distance. In contrast, the longest MMD distance was detected in the LFP features of the AD flu:KT aqueous, as shown in Fig. 8. This finding also brought us to the conclusive similarity of LFP responses obtained from the group of mice treated with KT syrup and AD flu.

V. DISCUSSION

Here, we discussed the results of three experiments to identify the gap in the conventional approach to LFP responses comparison and analysis. Then we addressed the contributions of the proposed approaches, which were ANet and the multi-task AE, in bridging the identified gap. Finally, we explained the feasible impact of the finding from the application point of view on the behavioral brain responses to the alternative AD substances for drug formulation; Kratom or KT extracted solutions.

Alternation of spectral power amplitudes is directly reflected in the changes in NeuroBios activity [2]. In addition, various experiments have presented the feasibility of using spectral power characteristics of LFP as a biomarker for substance profile classification [11]. Therefore, as demonstrated in Section IV-A, we conducted spectral power analysis and statistical testing. From the results in Table II, LFP spectral features that responded to KT syrup and KT alkaloids have significant differences in frequency responses in only a few brain regions when paired with LFP that responded to AD flu or standard substance for AD drug formulation. Therefore, we might infer that mice’s brains were influenced by KT syrup and KT alkaloids, closely to AD flu.

To utilize and enhance the findings of the conventional spectral power analysis, we proposed the AE-based LFP feature extractor or ANet to automatically detect the similarity of LFP responses from the interested substances compared to the reference drug (AD flu) which was AD flu in this study. According to Section IV-B, the defined similarity rate of LFP features extracted by ANet corresponding to KT syrup gave us about eight percent higher than those from KT alkaloids referred to LFP that responded to AD flu. These findings show the feasible applications of ANet in pre-screening the alternative substances which affect the mice’s brain similar to the standard or well-known substance in the future drug-formulated study.

Then, we extended ANet to be the multi-task AE for the multi-LFP response recognition, a more sophisticated task than anomaly or similarity detector. The benefit of this task was enhancing, visualizing, and measuring the difference between LFP responses of the candidate substances. Here, LFP responses of KT syrup and KT alkaloids were great examples. As reported in Section IV-A, the conventional approach could not give us a convincing conclusion in comparing LFP responses from the group of mice drugged by KT syrup, KT alkaloids, and AD flu. On the other hand, the proposed multi-task AE with qualitative and quantitative measures was quite promising in summarizing the LFP responses of KT syrup and KT alkaloids were much closer to AD flu than those of KT alkaloids.

Similar to revealing the similarity of LFP responses to KT syrup and AD flu for the first time, our investigation can inspire people interested in applying neural network-based computational modeling as innovative tools to the field of brain behavioral studies responses to the alternative formulation of novel drugs.
In this study, we illustrated the advantage of our proposed approach (ANet and extended ANet) that served as an extractor to automatically extract unknown discriminative features for substance similarity application on mice’s LFP features. However, the proposed approach still had a disadvantage that it was unable to know or understand how the model generated that effective feature. According to the limitation, the interpretable model could be further investigated to find which discriminative features are meaningful.

VI. CONCLUSION

This study proposed a neural network-based approach or ANet for comparing local field potential or LFP responses among the mice drugs with different substances. ANet automatically extracted the features from the unseen LFP responses and predicted the similarity rate to the reference or the standard responses used during the training process. Moreover, the extended ANet in the form of a multi-task AE presented the possibility of classifying multi-class LFP simultaneously. Here, we applied the proposed approaches to study the effect of Kratom, or KT extracted substances, compared to the standard AD drug via the mice’s brain activities. Both qualitative and quantitative assessments were used throughout the studies. As far as we concern, It was the first study in the literature. The outcomes convinced KT extracted using syrup induced the high similarity of LFP responses to the standard antidepressant drug or AD fluoxetine. In conclusion, we might infer that KT syrup is the potential candidate substance for an antidepressant drug formulation. However, further confirmation of the clinical and molecular scaled studies remains a future challenge.

REFERENCES

[1] D. Cheaha, N. Keawpradub, K. Sawangjaroen, P. Phukpattaranont, and E. Kumarnsit, “Effects of an alkaloid-rich extract from Mitragyna speciosa leaves and fluoxetine on sleep profiles, EEG spectral frequency and ethanol withdrawal symptoms in rats,” Phytochemistry, vol. 22, no. 11, pp. 1000–1008, 2015.

[2] D. Cheaha et al., “Effects of alkaloid-rich extract from Mitragyna speciosa (Korth.) havil. on naltrexone-precipitated morphine withdrawal symptoms and local field potential in the nucleus accumbens of mice,” J. Ethnopharmacol., vol. 208, pp. 129–137, 2017.

[3] J. Nukitram, D. Cheaha, N. Sengnon, J. Wangsintaweekul, S. Limswananchote, and E. Kumarnsit, “Ameliorative effects of alkaloid extract from Mitragyna Speciosa (Korth.) havil. leaves on methamphetamine conditioned place preference in mice,” J. Ethnopharmacol., vol. 294, 2022, Art. no. 114824.

[4] E. Kumarnsit, U. Vongvatcharanon, N. Keawpradub, and P. Intasaro, “Fos-like immunoreactivity in rat dorsal raphe nuclei induced by alkaloid extract of Mitragyna Speciosa,” Neurosci. Lett., vol. 416, no. 2, pp. 128–132, 2007.

[5] A. Saref et al., “Self-report data on regular consumption of illicit drugs and hiv risk behaviors after Kratom (Mitragyna Speciosa),” J. Psychoactive Drugs, vol. 416, no. 2, pp. 128–132, 2007.

[6] S. Assanangkornchai, A. Muekthong, N. Sam-Angsri, and U. Pattanasatayawong, “The use of Mitragynine Speciosa (‘Kratathom’), an addictive plant, in Thailand,” Substance use Misuse, vol. 42, no. 14, pp. 2145–2157, 2007.

[7] S. Buchhalter et al., “The antidepressant-like and analgesic effects of Kratom alkaloids are accompanied by changes in low frequency oscillations but not ΔFosb accumulation,” Front. Pharmacol., vol. 21, Art. no. 2002.

[8] N. F. Idyai et al., “Antidepressant-like effect of mitragynine isolated from Mitragyna Speciosa Korth in mice model of depression,” Phytochemistry, vol. 18, no. 5, pp. 402–407, 2011.

[9] E. Kumarnsit, N. Keawpradub, and W. Nuankaw, “Effect of Mitragyna speciosa aqueous extract on ethanol withdrawal symptoms in mice,” Fitoterapia, vol. 78, no. 3, pp. 182–185, 2007.

[10] S. Chitrakarn, P. Penjamras, and N. Keawpradub, “Quantitative analysis of mitragynine, codeine, caffeine, chlorphenteramine and phenylephrine in a kratom (Mitragyna Speciosa Korth.) cocktail using high-performance liquid chromatography,” Forensic Sci. Int., vol. 217, no. 1–3, pp. 81–86, 2012.

[11] R. Manor, E. Kumarnsit, N. Samerphob, T. Rujiralai, T. Puangpairote, and D. Cheaha, “Characterization of phar-maco-EEG fingerprint and sleep-wake profiles of Lavandula angustifolia Mill. essential oil inhalation and diazepam administration in rats,” J. Ethnopharmacol., vol. 276, 2021, Art. no. 114193.

[12] A. Korotcov, T. Tkachenko, D. P. Russo, and S. Ekins, “Comparison of deep learning with multiple machine learning methods and metrics using diverse drug discovery data sets,” Mol. Pharmacol., vol. 14, no. 12, pp. 4462–4475, 2017.

[13] M. Li, H. Gao, Y. Qi, and G. Pan, “A brain biometric-based identification approach using local field potentials,” in Proc. IEEE 43rd Annu. Int. Conf. Eng. Med. Biol. Soc., 2021, pp. 1116–1119.

[14] M. Hosny, M. Zhu, Y. Su, W. Gao, and Y. Fu, “A novel deep recurrent convolutional neural network for subthalamic nucleus localization using local field potential signals,” Biocybernetics Biomed. Eng., vol. 41, no. 4, pp. 1561–1574, 2021.

[15] A. Gogna, A. Majumdar, and R. Ward, “Semi-supervised stacked label consistent autoencoder for reconstruction and analysis of biomedical signals,” IEEE Trans. Biomed. Eng., vol. 64, no. 9, pp. 2196–2205, Sep. 2017.

[16] J. Tang, X. Shu, Z. Li, G.-J. Qi, and J. Wang, “Generalized deep transfer networks for knowledge propagation in heterogeneous domains,” ACM Trans. Multimedia Comput., Commun., Appl., vol. 12, no. 4, 2016, pp. 1–22.

[17] X. Shu, G.-J. Qi, J. Tang, and J. Wang, “Weakly-shared deep transfer networks for heterogeneous-domain knowledge propagation,” in Proc. 23rd ACM Int. Conf. Multimedia, 2015, pp. 35–44.

[18] P. Vincent, H. Larochelle, I. Lajoie, Y. Bengio, P.-A. Manzagol, and L. Bottou, “Stacked denoising autoencoders: Learning useful representations in a deep network with a local denoising criterion.,” J. Mach. Learn. Res., vol. 11, no. 12, pp. 3371–3408, 2010.

[19] A. Ditthapron, N. Banluesombatkul, S. Ketrat, E. Chuangsawanich, and T. Wilaiprasitporn, “Universal joint feature extraction for P300 EEG classification using multi-task autoencoder,” IEEE Access, vol. 7, pp. 68415–68428, 2019.

[20] P. Autthasan et al., “MIN2Net: End-to-end multi-task learning for subject-independent motor imagery EEG classification,” IEEE Trans. Biomed. Eng., vol. 69, no. 6, pp. 2105–2118, Jun. 2022.

[21] F. J. Martinez-Murcia et al., “EEG connectivity analysis using denoising autoencoders for the detection of dyslexia,” Int. J. Neural Syst., vol. 30, no. 07, 2020, Art. no. 2050037.

[22] X. Ran, W. Chen, B. Yvert, and S. Zhang, “A hybrid autoencoder framework of dimensionality reduction for brain-computer interface decoding,” Comput. Biol. Med., vol. 148, 2022, Art. no. 105871.

[23] G. Paxinos and K. B. Franklin, Paxinos and Franklin’s the Mouse Brain in Stereotaxic Coordinates. Norwell, MA, USA: Academic Press, 2019.

[24] J. Nukitram, D. Cheaha, S. Thawaii, N. Niyomdecha, and E. Kumarnsit, “Neural signaling of methamphetamine craving and seeking intensified by bupropion in the ventral tegmental area–cortico-accumbens circuitry in mice,” Addiction Biol., vol. 27, no. 06, 2022, Art. no. 13240.

[25] J. Nukitram, D. Cheaha, and E. Kumarnsit, “Spectral power and theta-gamma coupling in the basolateral amygdala related with methamphetamine conditioned place preference in mice,” Neurosci. Lett., vol. 756, 2021, Art. no. 135939.

[26] A. Gramfort et al., “MEG and EEG data analysis with MNE-Python,” Front. Neurosci., vol. 2013, Art. no. 267.

[27] J. Nukitram, E. Kumarnsit, and D. Cheaha, “A 1:1 ratio of cannabinoid: Tetrahydrocannabinol attenuates methamphetamine conditioned place preference in mice: A prospective study of antidopaminergic mechanism,” Brain Res. Bull., vol. 192, pp. 47–55, 2023.

[28] L. Van der Maaten and G. Hinton, “Visualizing data using t-SNE,” J. Mach. Learn. Res., vol. 9, no. 11, pp. 2579–2605, 2008.

[29] L. Butinack et al., “API design for machine learning software: Experiences from the scikit-learn project,” in Proc. ECML PKDD Workshop: Lang. Data Mining Mach. Learn., 2013, pp. 108–122.
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