Published in final edited form as:

IEEE Trans Neural Syst Rehabil Eng. 2018 November ; 26(11): 2115–2125. doi:10.1109/TNSRE.2018.2872919.

Large-scale Circuitry Interactions upon Earthquake Experiences Revealed by Recurrent Neural Networks

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Abstract

Brain dynamics has recently received increasing interest due to its significant importance in basic and clinical neurosciences. However, due to inherent difficulties in both data acquisition and data analysis methods, studies on large-scale brain dynamics of mouse with local field potential (LFP) recording are very rare. In this paper, we did a series of works on modeling large-scale mouse brain dynamic activities responding to fearful earthquake. Based on LFP recording data from thirteen brain regions which are closely related to fear learning and memory and the effective Bayesian connectivity change point model (BCCPM), we divided the response time series into four stages: “Before”, “Earthquake”, “Recovery”, and “After”. We first reported the changes in power and theta-gamma coupling during stage transitions. Then, a Recurrent Neural Network (RNN) model was designed to model the functional dynamics in these thirteen brain regions and six frequency bands in response to the fear stimulus. Interestingly, our results showed that the functional brain connectivities in theta and gamma bands exhibited distinct response processes: in theta band, there is a separated-united-separated alternation in whole-brain connectivity, and a low-high-low change in connectivity strength, however, gamma bands have a united-separated-united transition and a high-low-high alternation in connectivity pattern and strength. In general, our results offer a novel perspective in studying functional brain dynamics under fearful stimulus and reveal its relationship to the brain’s structural connectivity substrates.

Keywords

brain dynamics; large-scale LFP recordings; fear conditioning; recurrent neural network

I. Introduction

BRAIN dynamics has recently received increasing interest due to its significant importance in basic and clinical neurosciences. There are accumulating evidences [1-4] indicating that brain activities are under dramatic temporal changes at various time scales. For instance, it has been found that each cortical brain area runs different “programs” according to the cognitive context and to the current perceptual requirements [2], where intrinsic cortical circuits mediate the moment-by-moment functional state changes in the brain [2]. Inspired by the important observations on the functional brain dynamics from prior research studies [1-4], there have been many works aiming to quantitatively characterize the temporal dynamics and their transitions. In general, these literature studies have significantly advanced our fundamental understanding of brain dynamics. However, these prior studies might have limitations in either data acquisition or data analysis methods, which motivates other researchers to explore new data acquisition methods and/or novel data modeling approaches.

Overall, many of previous studies used either fMRI data [5-8] or EEG data [9-12], however, there are several methodological and technical limitations in these fMRI/EEG-based brain dynamics studies. Specifically, fMRI measures the blood oxygen level dependent (BOLD) changes, which is not a direct measurement of neural activities. Meanwhile, fMRI is known to be confounded by non-neuronal factors, such as head motion, as well as physiological respiratory- and cardiac-related fluctuations [13-15]. Besides, fMRI-based brain dynamics study is significantly limited by its temporal resolution and the lack of time series data with

sufficient length, which results in the lack of sufficient temporal brain dynamic information. Moreover, many real-world experiences, such as how the brain encodes earthquake, can't be studied easily with the current setting and devices.

On the contrary, EEG data has much better temporal resolution and much longer acquisition length, but it only measures the scalp electric potential field, which lacks the spatial accuracy for more precise neuroscience studies [16]. On the other hand, microelectrodes are the gold-standard method with its high temporal resolution and cellular-level neural activities. Compared with the macro-scale functional neuroimaging methods such as fMRI or EEG, local field potential (LFP) [17-20] records the micro-level excitatory and inhibitory neuronal activities in milliseconds. Consequently, brain dynamics and its transitions derived from LFP data could be more in freely behaving animals over a long period of time. Therefore, this work aims to apply multisite LFP to study fear memory formation. Given the fact that earthquake evokes strong long-term fear memory, there are no fMRI and EEG study on this important topic, we set out to examine large-scale circuitry dynamics as the brain encodes earthquake experiences.

From a data analysis perspective, windowed method [6, 8, 21, 22], especially sliding window method, has been among the most widely used approaches in brain dynamics analysis. For this category of method, a window is moving along the time series and a special indicator is calculated for each window. Different studies have used various window lengths, but the length is typically constant during the analysis. The choice of window length is of vital importance for sliding window approaches since it effects the ability of extracting relevant information from the data and the interpretation of the results. Long windows achieve the traditional measures of average dynamics by averaging the signal over longer periods; short windows are more sensitive to transient changes but they could introduce more noises [23]. Unfortunately, the duration of a typical brain state is typically unknown, which motivates researchers turn to other methods to identify applicable window sizes. In this scenario, change point method, whose goal is to detect when a change of brain state occurs based on the data properties, deals with the abovementioned challenges by choosing an appropriate window length. In the detection of change points, simpler approaches, such as signal amplitude clustering, or more complicated methods, like hidden Markov models, can be applied [24-26]. Also, the change points of large-scale brain activity can be identified by using the relationships between the signals from different brain areas [6, 27, 28]. To some extends, change point method can be considered as a windowed approach in which window length is adaptively determined according to the signal properties [29], which is adopted in this work.

Recently, Recurrent Neural Networks (RNNs) have shown particularly outstanding performances in many scientific research areas, such as handwriting recognition [30, 31], language modeling [31, 32], machine translation [33], and speech recognition [34], which involve dependent input data sequences. Although there are various approaches used in modeling temporal sequence dependencies, such as Markov model [24-26] and some statistic methods, however, these models are all low-order and they can hardly extract features maintained in long term memory. A prominent feature of RNNs is that they can easily and effectively capture both short and long term temporal dependencies in data

sequences and model the inner dependent relationships using their internal memories. To realize this characteristic, RNNs maintain memory cells to preserve the information of the past sequences and learn when and how to restore these memories to make predictions, rather than predicting based only on local neighborhoods in time. Therefore, RNNs can inherently acquire recurrent information flow of ongoing dynamics, and have capabilities to approximate any dynamical system. Human brain is a deep and complicated neural network, in which feedforward, lateral, and feedback connections are ubiquitous. Recurrent Neural Networks (RNNs), where units are connected in cycles, are much more similar to biological neuronal networks than other structures. A few attempts of using RNNs in neural encoding [35-37] and responding [38] have shown that RNNs are very appropriate in brain dynamics studies. Therefore, in this work, we are inspired to employ RNNs to model the LFP time series data to investigate functional brain dynamics.

In brief, in this paper, we employ a state-of-the-art 512-channel tetrode system, which allows recording LFP signals simultaneously over a dozen cortical and subcortical regions during earthquake events in freely behaving mice [20]. Using this system, LFP data covering trials of fearful stimulus in thirteen distinct brain regions of freely-behaving mice were recorded. Via a highly effective Bayesian connectivity change point model (BCCPM) [6, 27], significant change points were detected in each response series, by which we divided the response process into four stages: “before”, “Earthquake”, “Recovery”, and “After”. During the alteration of stages, changes in power and theta-gamma coupling occurred, which are believed to play a key role in neural information processing. As expected, our results show that the spectral power increased when fearful stimulus was implemented and then decreased gradually to normal. Then, with the LFP time series and the BCCPM-derived stage labels, a RNN model was designed and applied to explore and model how each brain region and frequency band reacts to the fear stimulus. It turned out that all thirteen recorded brain regions were prominently sensitive to the fear stimulus, and large scale functional brain dynamics emerged in all six frequency bands (delta, theta, alpha, beta, low gamma, and high gamma). In addition, compared with autocorrelation approach of adaptive autoregressive (AAR) classifier [39, 40] and non-temporal method of support vector machine (SVM), RNN model performed much better in recognition of four responding stages. Finally, we employed functional brain connectivity to quantitatively characterize the large-scale temporal functional dynamics, and found that there were distinct connectivity patterns existing in theta and gamma bands. These patterns were revealed and interpreted in a neuroanatomic context, e.g., there were significant differences in pattern transition tendency: during earthquake experiences, connectivity strength increased in theta band, and decreased in gamma band. In general, our work offers a novel perspective in studying functional brain dynamics and reveal its relationship to the brain’s structural connectivity substrates during fear memory processes.

II. Materials and Methods

A. Data Acquisition via 512-Channel Tetrode System

As tetrodes offer a superior spike-sorting capacity, we designed and constructed a 512-channel headstage system that could hold 128 tetrodes (512 channels). We selected thirteen

distinct brain regions based on their roles relating to the processing of fear-conditioning memory [20]. These brain regions and their abbreviations used in this paper are as follows: hippocampal CA1 (CA1), dentate gyrus (DG), somatosensory cortex trunk (S1Tr), somatosensory cortex hind limb (S1HL), retrosplenial granular cortex (RSG), retrosplenial agranular cortex (RSA), subiculum (S), perirhinal cortex (PRh), lateral entorhinal cortex (LEnt), secondary auditory cortex (AuV), Cg1 and Cg2 sub-regions of the anterior cingulate cortices (Cg1 & Cg2), prelimbic cortex (PrL). The electrode positions on the microdrive headstage are pre-calibrated according to coordinates provided by the Mouse Brain Atlas [41]. Thirteen modular bundles of tetrodes targeting thirteen brain regions are used to record the neuronal activities simultaneously as shown in Fig. 1(a). According to the sizes and depths of these brain regions, each modular bundle consists of either 8 or 16 tetrodes (32 or 64 channels). Once the above tetrode modules are constructed, a sequential-insertion strategy is applied to implant the 512-channel system into the adult male mice (4- to 6-month old with a body weight of 35–40 g). The surgery can be completed in about five hours for each mouse. To solve the modules' and cables' weight issue, a few large helium balloons are tethered to the cables to relieve weights. For chronic recordings, we typically allow the mice that underwent surgery to recover for 3~5 days before the experiment begins.

Neural-spike activities and LFPs are recorded once the 512-channel cables are connected to the 512-channel Plexon multiplex-recording system [42, 43], and a segment of recording signals are shown in Fig. 1(b). Since LFP tends to be similar within nearby tetrode channels, one channel recording is selected from each tetrode. Therefore, this 512-channel LFP-recording setup provides us a total of 128 channels of signals. The stability of the ensemble recordings can be verified by comparing waveforms and interspike intervals at the beginning, during, and after the experiments. As our 512-channel system can hold electrodes in position for many days, recording stability is verified by the PCA-based spike-sorting patterns, measured by “isolation-distance” and “L-ratio”. The analysis shows that the units recorded can maintain good separation and stability over days or even weeks.

To investigate the large-scale and multi-structure dynamics in the mouse brain during fear stimulus, we subjected the mice to a fearful episode namely earthquake. Previous studies have shown that earthquake-like events are fearful to mice and can trigger induced diverse changes in the CA1 region of the mouse hippocampus [44, 45]. In the present study, we did earthquake evoke firing changes in a brain-wide manner. We subjected the mice to an earthquake (0.5s in duration) ten times and monitored how neurons responded across all of the thirteen brain structures.

In this paper, based on the upper and lower ranges of previous studies [46, 47], we separated six commonly used frequency bands: delta band (0~4Hz), theta band (4~8Hz), alpha band (8~12Hz), beta band (12~30Hz), low gamma band (30~60Hz), and high gamma band (60~150Hz).

B. Recurrent Neural Networks

RNNs have the inherent architecture with dynamics, in which units are connected in cycles. This distinct architecture is similar to biological neuronal networks, where lateral and feedback interconnections are widespread. The internal state of RNN preserves a memory,

which represents the stimulus history so far. RNNs have been applied successfully in many diverse sequence modeling tasks [30-34], and a generic RNN model is shown in Fig. 2(a). An RNN preserves a hidden state $\mathbf{c}^t$ and at each time step t , the nonlinear block uses the previous hidden state $\mathbf{c}^{t-1}$ and the current input $\mathbf{x}^t$ to produce a new hidden state $\mathbf{c}^t$ and an output $\mathbf{h}^t$.

If we use the nonlinear block shown in Fig. 2(b), a specific and simple model - a vanilla RNN with one hidden layer would be obtained. The recursive equation for a vanilla RNN, which is illustrated in Fig. 2(b), is

$$\mathbf{h}^t = \tanh(\mathbf{U}\mathbf{h}^{t-1} + \mathbf{W}\mathbf{x}^t + \mathbf{b}) \quad (1)$$

here, $\mathbf{U}$, $\mathbf{W}$, and $\mathbf{b}$ are free parameters that are shared over time. For the vanilla RNN, we have $\mathbf{c}^t = \mathbf{h}^t$. The height of $\mathbf{h}^t$ is a hyperparameter and is referred to as the number of hidden units.

Typically, vanilla RNNs are very difficult to train due to the vanishing gradient problem [48]. In response, LSTM [49] and GRU [33] were specifically designed to overcome this problem and have since become the most widely-used RNN architectures.

Each LSTM [49] unit has a cell state that acts as its internal memory by storing information from previous time points. The contents of the cell state are controlled by the gates of the unit and in turn determined its outputs. The gates are implemented as multiplicative sigmoid functions of the inputs of the unit at the current time point and the outputs of the unit at the previous time point, to determine the amount of information to store, forget or retrieve at each time point. The first-layer hidden states of an LSTM unit are defined as follows:

$$\mathbf{h}^t = \mathbf{o}^t \odot \tanh(\mathbf{c}^t) \quad (2)$$

$$\mathbf{o}^t = \sigma(\mathbf{U}_o \mathbf{h}^{t-1} + \mathbf{W}_o \mathbf{x}^t + \mathbf{b}_o) \quad (3)$$

where $\odot$ denotes elementwise multiplication, $\mathbf{c}^t$ is the cell state, and $\mathbf{o}^t$ are the output gate activities. The cell state maintains information about the previous time points. The output gate controls what information will be retrieved from the cell state. The cell state of an LSTM unit is defined as:

$$\mathbf{c}^t = \mathbf{f}^t \odot \mathbf{c}^{t-1} + \mathbf{i}^t \odot \tilde{\mathbf{c}}^t \quad (4)$$

$$\mathbf{f}^t = \sigma(\mathbf{U}_f \mathbf{h}^{t-1} + \mathbf{W}_f \mathbf{x}^t + \mathbf{b}_f) \quad (5)$$

$$i^t = \sigma(U_i h^{t-1} + W_i x^t + b_i) \quad (6)$$

$$\tilde{c}^t = \tanh(U_c h^{t-1} + W_c x^t + b_c) \quad (7)$$

where f^t are the forget gate activities, i^t are the input gate activities, and $\tilde{c}^t$ is an auxiliary variable. Forget gates control what old information will be discarded from the cell states. Input gates control what new information will be stored in the cell states. Furthermore, U_f , U_i , U_c and W_f , W_i , W_c are the weights and b_f , b_i , b_c are the biases that determine the behavior of the gates (i.e., the learnable parameters of the model).

The GRU [33] units are simpler alternatives to the LSTM units. They combine hidden states with cell states and input gates with forget gates. The first-layer hidden states of a GRU unit are defined as follows:

$$h^t = (1 - z^t) \odot h^{t-1} + z^t \odot \tilde{h}^t \quad (8)$$

$$z^t = \sigma(U_z h^{t-1} + W_z x^t + b_z) \quad (9)$$

$$r^t = \sigma(U_r h^{t-1} + W_r x^t + b_r) \quad (10)$$

$$\tilde{h}^t = \tanh(U_h (r^t * h^{t-1}) + W_h x^t + b_h) \quad (11)$$

where z^t are update gate activities, r^t are reset gate activities and $\tilde{h}^t$ is an auxiliary variable. Like the gates in LSTM units, those in GRU units control the information flow between the time points. As before, U_z , U_r , U_h and W_z , W_r , W_h are the weights and b_z , b_r , b_h are the biases that determine the behavior of the gates (i.e., the learnable parameters of the model).

In this paper, to better capture temporal dependency and model the corresponding temporal dynamics, a four-layer architecture with two recurrent layers is designed and applied, as shown in Fig 3. Adjacent layers are fully connected, and the connections are forward. Two recurrent layers have the same structure, and each is internally fully interconnected, as shown in Fig. 4, so that various types of temporal dependent could be used. The second-layer hidden states are defined similarly to the first-layer hidden states except for replacing the input with the first-layer hidden states. In the case of multiclass classification, we use a

linear layer to transform $\mathbf{h}^t$ to appropriate size n_y and apply a softmax layer to obtain a vector of class probabilities:

$$\hat{\mathbf{y}}_t = \text{softmax}(\mathbf{U}_y \mathbf{h}^t + \mathbf{b}_y) \quad (12)$$

$$p(\mathbf{y}_{tk} = 1 \mid x_1, x_2, \dots, x_t) = \hat{\mathbf{y}}_t \quad (13)$$

where $\text{softmax}(\mathbf{x}) = \exp(\mathbf{x}) / \sum_i \exp(x_i)$.

In this paper, the RNN model is implemented with Tensorflow. Truncated backpropagation through time is employed in conjunction with AdamOptimizer to train the models by iteratively minimizing the overall cross entropy between the true labels $\{\mathbf{y}\}$ and the predicted labels $\{\hat{\mathbf{y}}\}$. Dropout [50] is used to regularize the hidden layers. The epoch in which the validation performance is the highest is taken as the best model. The RNN model was run on the computing platform with two GPUs (Nvidia GTX 1080 Ti, 12G Graphic Memory) and 64 G memory.

C. Representations of Theta-Gamma Modulation and Brain Functional Connectivity

Theta and gamma oscillations coordinate the timing of multiple inputs to neurons and have been linked to information processing and the dynamics of encoding and retrieval. Modulations of low and high gamma envelope amplitude by theta phase were measured respectively. We used vector strength [51] to indicate the degree of modulation of the gamma envelope to the phase of theta, and the calculation is as follow:

$$VS = \left| \int_0^{2\pi} e^{i\varphi} p(\varphi) d(\varphi) \right| \quad (14)$$

Theta phase (-180° – 180°) was divided into eighteen 20° intervals $p(\varphi)$. Then, the mean of low and high gamma envelope amplitude over each phase bin was normalized by dividing the summation of all bins, denoted as $d(\varphi)$. Since higher amplitude of gamma centered at certain phases of theta yields a higher value than if gamma amplitude is uniform across theta phase, vector strength could be used to tell if the gamma amplitude envelope is concentrated within certain phase bins [52].

In many previous studies [1-4], it has been shown that functional brain activities are under dramatic temporal changes at various time scales. Here, the pairwise functional interaction is defined as the Pearson correlations [53-55] between every pair of the LFP time series segments as follows:

$$R_{i,j,t} = \text{corr}(\mathbf{TS}_{i,t}, \mathbf{TS}_{j,t}), \quad R_{i,j,t} = 0, \quad \text{if } i = j; \quad (15)$$

$$FC_t = \{R_{i,j,t} \mid i, j \in (1, 13)\} \quad (16)$$

where FC_t denotes the FC within the t -th LFP time series segment, which is a set of correlations from the congregation of all $R_{i,j,t}$ over each combination of i and j , and thus is a symmetrical connectivity matrix with the dimension of 13×13 , $TS_{i,t}$ denotes the t -th LFP time series segment extracted from the i -th region.

III. Results

A. Four Stages Separated by Change Points

As aforementioned, brain states are typically undergoing temporal dynamic changes. Inspired by state-like behavior of brain activities, we applied BCCPM [56] on the LFP time series data to detect the change points. BCCPM (detailed in Supplementary Materials) is proposed to analyze the joint probabilities among brain regions between different time periods and statistically determine the boundaries of temporal blocks to estimate the change points. Intuitively, the determined change points represent the transitions of functional interaction within the brain networks and can be used to investigate temporal functional brain dynamics. In this paper, we applied BCCPM on LFP series with various length (1000~6000 time points) around earthquake stimuli, and three change points were detected in each stimulus process, as shown in Fig. 5(a). Therefore, the LFP time series around each stimulus was divided into four segments.

To assess how earthquake stimulus affected the brain activities, the power spectral density of each brain area during four stages was represented as decibels (dB) relative to $1 \mu V$, as shown in Fig. 5(b). It is easy to appreciate that when the stimulus is implemented, each of the thirteen brain regions would activate and the power of LFP signals increase. As the earthquake stimulus is over, each region drops down and the power decreases gradually. The response to fear stimulus of earthquake is accompanied with variation of power, based on which we called four stages “Before”, “Earthquake”, “Recovery” and “After”, respectively, as shown in Fig. 5(a). Because the “After” stage is also the “before” stage of next stimulus, so these four stages indicate a circuitry interactions of brain dynamics.

In this paper, the recover stage is eliminated, as it is too short (about 200ms) to cover a whole theta period, and modulation index of the gamma amplitude across theta phase was calculated for both the low and high gamma bands. Comparing distribution of each stage, it is easy to observe that both low and high gamma amplitudes changed with theta phase in “Earthquake” stage, which is largely absent in the “Before” and “After” stage, as shown in Fig. 6(a). Meanwhile, there is a great similarity between low and high gamma in modulation during stimulus, as their distributions are quite alike. It is apparent that different regions run different modulation distributions, in spite that they work in same frequency band.

B. Circuitry Interactions Modeled by RNN in Regions and Frequency Bands

As introduced beforehand, it is easy to find that BCCPM is a statistics approach which aims to detect change points by joint probabilities among brain areas, rather than a system which

can model brain dynamics. Therefore, we proposed a four-layer RNN model for brain dynamics modeling.

In RNN model, the modeling ability has close relationship with the number of hidden layer. In multi-layer RNN model, different layers can preserve different time-scale memories, that bottom layer has very short time scale, whereas higher layers maintain longer memories [57]. Therefore, to model multiple time scales of brain dynamics, we applied multilayer structure. In Fig. 7(a), RNNs achieve better performances with more hidden layers, however, the improvement becomes smaller with the increase of layer number. In Fig. 7(b), the time cost is in proportion to the number of hidden layers. This is because the number of parameters and computational costs depend linearly on this RNN model. Therefore, balancing the accuracy and time cost, we chose two recurrent hidden layer finally. Moreover, many previous literature studies [38, 58] used two-layer recurrent hidden layers and achieved good results. Besides, the type and number of cell units also largely influence the performance of the network, and more units generally have stronger capability to represent the properties of datasets. However, too many units may also cause overfitting problems. By comparing the prediction results of RNNs composed of different types and different numbers of cell units in test trials, as shown in Fig. 7(c), we finally employed 128 GRU cells in each recurrent layer.

With the segmentation of change points detected by the BCCPM, the stimulus series can be labelled with 4 states: “Before” and “After” were label as “0”, “Earthquake” was “1”, and “Recovery” was marked as “2”. The input series of the brain region study and frequency band study are shown in Fig. 8. The input series are made up of two parts, amplitudes and phases. Analyzing amplitude and phase separately can enrich content of input information, and help the model achieve better performance. The amplitude and phase series were separated from raw signals by Hilbert transform in MATLAB (MathWorks).

During training process, rather than using the whole sequence, we cut sequence fragments with random length (40%~70% of the whole sequence length) from random location of all stimulus series, and fed them to the RNN model. By this approach, we created huge amounts of distinct sequences with different lengths, which helped to train a better model. In our work, different parameter initializations and random sequence fragments had great influences on training convergence, so that convergence procedure of each training process is quite different. Therefore, to obtain stable results, we stopped training after 1,000 epochs, when convergence was surely achieved. Since the fearful earthquake stimulus was repeated 10 times, 10-fold cross validation strategy was used to train the model and validate the results. We implemented the computation in parallel, and all the tasks of one brain region or a frequency band could be finished within two hours.

To make a comparison, we also modeled this circuitry interaction with an autocorrelation method of adaptive autoregressive (AAR) classifier and a non-temporal approach of Support Vector Machine (SVM). In this paper, SVM was based on RBF kernel, and the parameters of both AAR and SVM were finely tuned. The recognition results of RNN model, AAR classifier and SVM based on each brain region are shown in Fig. 9. The recognition results of RNN match the ground truth very well, and AAR classifier also achieves good

performance. In contrast, the recognitions of SVM are decentralized, and we can hardly differentiate the four stages of response. To quantitatively illustrate the recognition performances, we applied the correlation between recognized label series and ground truth label series to indicate recognition accuracy, and the averaged accuracy results of ten stimulus segments are shown in Fig. 10. It is easy to appreciate that RNN's recognition accuracies of all brain regions reach over 80%, outperforming AAR classifier and SVM. AAR classifier performs a little worse than RNN, but still much better than SVM, whose recognition accuracies are only around 60%. Besides, all thirteen brain regions show great sensitivity to earthquake stimulus. These results strongly suggest that the RNN model has great advantages in modeling brain temporal dynamics, and the thirteen brain regions we selected respond to fearful earthquake stimulus accurately.

Similar results also can be found in six frequency bands, as shown in Fig. 11 and Fig. 12. In Fig. 12, it can be easily observed that RNN model performs the best, and the accuracy of RNN increases from 70% to 90% with the increase of frequency. Meanwhile, it is interesting to observe that AAR classifier and SVM achieve their best performances in alpha band, and AAR classifier recognizes more accurate than SVM except in delta band. In addition to the advantages in modeling brain temporal dynamics of RNN, these results also demonstrate that the effects of earthquake stimulus exist in all frequency bands.

The brain is a deep and complicated neural network, in which feedforward, lateral, and feedback connections are ubiquitous. Unsurprisingly, non-temporal model SVM, which can only map input vector to output label at one time point, can hardly capture temporal dependency hidden in time series. AAR classifier relies only on a small range of memory to make a classification, and cannot adaptively extract valuable dependency from all history. In contrast, the RNN model we proposed, in which units are connected in cycles, is capable to maintain long short term memory and capture sequence dependency. Therefore, RNN model is much more similar to biological neuronal networks than other methods or models. In other words, SVM is a static function approximator, AAR classifier adds a sliding window to a static function approximator, while RNNs are universal approximators of dynamical systems. In our work, the outstanding performances in thirteen brain regions and six frequency bands indicate the efficiency and effectiveness of RNN in the modeling of brain LFP signal time series.

C. Brain Functional Connectivity in Different Stage

Based on the change points detected via the BCCPM, the whole LFP time series of each fearful episode are divided into four segments, as shown in Fig. 5(a). In our experiment, distinct functional connectivity pattern can be observed in each stage. In the theta band, as shown by connectivity matrices in Fig. 13, the whole-brain connectivity underwent a transient temporally coordinated activation process, with connectivity strength enhanced during earthquake and then weaken to the basal level. Specifically, in "Before" stage, the brain runs in a normal pattern, in which there are three distinctive groups of connectivities: Group-1 (colored in red) is composed of interconnections between 4 regions (CA1, DG, S1Tr, S1HL, RSG, RSA and S); Group-2 (colored in blue) involves interactions of S1Tr, S1HL, AuV, Cg1, Cg2 and PrL; Group-3 (stressed in orange) includes connections between

PRh, LEnt, as well as AuV. Group-1 and Group-2 share regions of S1Tr and S1HL (colored in magenta), and AuV (stressed in green) appears in both Group-2 and Group-3. Then, when the fearful Earthquake is executed, all connectivity pairs are enhanced to the top, and all connectivity groups combines into one, indicating that all thirteen regions respond to fearful event synergistically. However, after stimulus, the strength of some connectivity pairs decrease by degrees, as shown by the color changes of connectivity matrix in Fig. 13. After “Recovery” period, the connectivity pattern of thirteen regions in “After” stage returns to normal, near same as the patterns in “Before” stage. From the alternation of brain connectivity patterns, it is easy to appreciate the response process in theta band, that three connectivity networks typically work respectively in normal state, with a few brain regions as sharing nodes, such as S1Tr and S1HL within Group-1&2, as well as AuV within Group-2&3, which facilitate the communication between networks. When the earthquake occurred, all regions were activated in a highly coordinated manner, with connectivity strength transiently enhanced. Then this coordinated pattern broke down back into three segregated networks gradually with connectivity strength decreased.

To investigate the role of each region, a statistical comparison of connectivity strength was implemented, shown as the connectivity strength summation histogram. The results reveal that region PRh and LEnt have relatively low correlations with other regions. These two brain regions are more likely to work independently. The cooperation of different regions, as well as their relative independences, is largely due to their structural connections in brain. In the sections of Fig. 13, it is easy to appreciate that those regions, which locate adjacently or near, more tend to affect each other and work together.

Though there is an apparently separated-united-separated response process of functional connectivities in theta, it is quite different in gamma. On the contrary, the responses of gamma bands differed from the theta. The gamma connectivity strength decreased during earthquakes and then recovered to the basal state. As the connection patterns of low gamma shown in Fig. 14(a), in “Before” stage, there are only two connectivity groups: Group-1 (colored in red) includes connectivities between 10 regions (CA1, DG, S1Tr, S1HL, RSG, RSA, AuV, Cg1, Cg2 and PrL); Group-2 (stressed in blue) only contains three regions of S, PRh and LEnt, as well as their connections. These two connectivity networks constitute the functional brain pattern in normal state. When the fearful earthquake is executed, the connectivity groups change. Specifically, Group-1 is split in two, which CA1, DG and AuV separate from the other regions in Group-1 and make up a new group (marked in orange), as shown in subgraph of “Earthquake” stage. Meanwhile, the strength of whole-brain connectivities decrease during earthquake. As the stimulus fades away, the separated parts tend to combine and the connectivity strength increases by degree during “Recovery” stage, until the pattern and the strength of connectivity recover to normal. Furthermore, it is also very easy to appreciate from the histograms that S, PRh and LEnt are the regions with the weakest mutual correlations with the others. Region S even has negative correlation strength. Except for a few subtle differences, the characteristics of functional brain connectivities in high gamma are almost the same as those in low gamma, as shown in Fig. 14(b).

In summary, we provide the first large-scale brain dynamics in response to fearful earthquake event. We found that brain connectivity pattern and connectivity strength

exhibited coordinated changes across many frequencies. Most notably, connectivity strength in the theta band showed temporally coordinated increases during earthquakes, whereas connectivity strength in the gamma bands exhibited transient suppression.

IV. Discussion

In our study, we examined earthquake-induced brain-wide LFP temporal dynamics in freely-behaving mice by state-of-the-art 13-site and 512-channel tetrode recording system. With the change points detected by effective Bayesian connectivity change point model, LFP response processes of each trial were divided into four stages: “Before”, “Earthquake”, “Recovery”, and “After”. As expected, spectral power rose in “Earthquake” stage, and fell to normal during stage of “Recovery”. Meanwhile, during fearful earthquakes, theta-gamma coupling emerged gradually, and theta-gamma modulation differed in regions. Via RNN models, we verified that all thirteen brain regions we studied all played roles in responding to fearful stimulus, and brain LFP dynamics was revealed in all six frequency bands. Then large-scale temporal dynamics was quantitatively characterized via functional brain connectivity. Distinct connectivity patterns and unique transition tendencies in theta and gamma bands were revealed, and significant functional connections were interpreted.

However, this work can be further enhanced in the following directions. First, even though thirteen distinct brain regions and 512 channels are state-of-the-art in mouse LFP studies, there are still many other regions remaining unexploited, which are also thought to play important roles in fear memory. More advanced LFP recording methods, or sophisticated and effective algorithms should be designed and employed to obtain more LFP data from the underexplored brain areas. second, in this paper, we explored the mouse brain dynamics under fearful (earthquake) situation. similarly, with effective Bayesian connectivity change point model and recurrent neural network, many other types of fearful events, both unconditioned and conditioned tasks (*i.e.* contextual, cued, or trace fear conditioning) [59, 60], should be studied in the future. These experiments will enrich our understanding of how the brain encodes not only specific fear memories but also generalized knowledge [61, 62].

In summary, large-scale, multi-sites in vivo recording techniques have offered a new avenue to gain the critical insights into brain dynamics and functional connectivity in freely behaving animals. We have uncovered a set of cross-region LFP interactions related to encoding of earthquake experiences. Moreover, we showed that the RNN has inherent advantages in modeling brain-wide LFP temporal dynamics, compared with other models. We envision that this combined approach can be valuable to further investigate how the brain generates perception, memories and behaviors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

H Wang was supported by the Fundamental Research Funds for the Central Universities.

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Fig. 1.

The design of 512-channel tetrode arrays for brain-wide neural recording in mice. (a) Schematic drawing for the 512-channel tetrode device for recording in a total of thirteen different brain regions in mice. The scales are marked by black bars. (b) Large-scale local field potentials (LFP) simultaneously recorded from thirteen different brain regions.

Fig. 2.

Illustration of RNN models. (a) Generic RNN model. (b) Basic nonlinear cell unit. (c) Long short-term memory (LSTM) unit. (d) Gated recurrent units (GRU). Squares indicate linear combination and nonlinearity. Circles indicate elementwise operations. Gates in the units control the information flow between the time points.

Fig. 3.

Overview of recurrent neural network for brain dynamics modeling. The amplitude and phase of brain LFP sequences are separated and fed to the network model. Two recurrent layers cascade to model temporal dynamic dependency. A softmax classifier is arranged for the response stage prediction.

Fig. 4.

Interconnections in recurrent hidden layer. (a) Neurons in recurrent layer are fully interconnected. (b) The connection pattern after unfolding along time. New hidden states can be influenced by all former states.

Fig. 5. Results of BCCPM. (a) Change point detection in the LFP time series of each mouse via the BCCPM. Stimulus situations are shown at the top, and four stages are separated at the bottom. (b) Histograms of power in each stages. In every brain region, power value grows during stimulus and then decreases gradually to normal, and power in “Earthquake” stage is the highest.

Fig. 6.

Theta phase modulation of gamma envelope. (a) (b) Distributions of theta phase modulation of the low gamma and high gamma amplitude envelope of “Before”, “Earthquake”, “After” stage in CA1 area. (c) (d) Distributions of theta phase modulation of the low gamma and high gamma amplitude envelope of the other 12 regions in “Earthquake” stage, and distributions are various.

Fig. 7.

Illustration of the influences of hidden layer and cell unit on modeling performance. (a) Influence of hidden layer number on modeling accuracy. (b) Influence of hidden layer number on time cost. (3) Influence of recurrent cell unit on modeling accuracy.

Fig. 8. Illustration of the input series. (a) The input series of brain area study. (b) The input series of frequency band study.

Fig. 9.

Recognized label series of RNN, AAR classifier and SVM based on thirteen brain regions, respectively. Each subgraph is composed of four label series, which from top to bottom are: the ground truth series, and the recognized label series of RNN, AAR classifier, and SVM.

Fig. 10.
Recognition accuracies of RNN, AAR classifier and SVM based on thirteen brain regions respectively.

Fig. 11.

Recognized label series of RNN, AAR classifier and SVM based on six frequency bands respectively. Each subgraph is composed of four label series, which from top to bottom are: the ground truth series, and the recognized label series of RNN, AAR classifier, and SVM.

Fig. 12.
Recognition accuracies of RNN, AAR classifier and SVM based on six frequency bands respectively.

Fig. 13.

Illustration of functional brain connectivity dynamics in theta band. Functional brain connectivity matrix of each stage is shown at top left corner of subgraph, and it is color-coded according to the strength of functional interaction between the ROI labeled by the column index, to the ROI labeled by the row index. Connectivity strength summation histogram is located at the top right. Functional brain connections over brain section are illustrated at the bottom, where distinct cooperative groups are stressed in different colors.

Fig. 14.

Illustration of functional brain connectivity dynamics in gamma bands. (a), (b) illustrates the alternations of functional brain connectivity in low gamma band and high gamma band, respectively. Functional brain connectivity matrix of each stage is shown at top left corner of subgraph, and it is color-coded according to the strength of functional interaction between the ROI labeled by the column index, to the ROI labeled by the row index. Connectivity strength summation histogram is located at the top right. Functional brain connections over brain section are illustrated at the bottom.