The Spike-timing-dependent Plasticity Function Based on a Brain Sequential Learning System Using a Recurrent Neuronal Network

Genki Ogata, Kiyohisa Natsume, Satoru Ishizuka, Hatsuo Hayashi

Abstract:

This paper examines the spike-timing-dependent plasticity (STDP) at the synapses of the medial entorhinal cortex (EC) and the dentate gyrus (DG) in the hippocampus. The medial and lateral ECs respectively convey spatial and non-spatial information to the hippocampus, and the DG of the hippocampus integrates or binds them. There is a recurrent neuronal network between the EC and the hippocampus called the EC-hippocampus loop. A computational study has shown that using this loop and STDP phenomena at the recurrent EC synapse, sequential learning can be accomplished. But the STDP functions at the synapses of the EC and DG have not yet been studied by neurophysiological experiments. Experiments on STDP phenomena were performed in rats. The STDP function was asymmetrical in the EC synapse and symmetrical in the DG. The medial EC mainly processes the time-series signals for spatial information about visual landmarks when a rat is running in an environment, the lateral EC processes their features, and the DG binds or integrates the information on the positions and features of the landmarks. Thus, the EC-hippocampus loop processes sequential learning of spatial and non-spatial information in parallel, and the DG binds or integrates the two kinds of signals. A system based on this biological phenomenon could have similar characteristics of parallel processing of object features and positions, and their binding.

Keywords: *hippocampus, entorhinal cortex, STDP function, brain science.*

1. Introduction

Animals live in a temporal world. They can experience several events and store them as episodic memories using their brains. They can also sense a sequence of the events and memorize the sequence. In the engineering field, memorization, i.e., sequence learning, is processed as a recurrent neural network [1]. Michael Jordan developed a recurrent network and applied it to word recognition and the production of speech, etc. [2]. But how does the brain itself process such sequence learning?

The entorhinal cortex and hippocampus in the brain are thought to be involved in sequence learning. The hippocampus processes episodic memory. In episodic memory, many sensory signals flow into the hippocampus one by one. The sensory signals are processed in the cortex first. They then flow into the hippocampus *via* the entorhinal cortex (EC) [3]. For example, when a rat is running in an environment where some visual landmarks are located, spatial information, which is processed in the parietal cortex, first enters into layer II of the medial EC (MEC) and flows into the hippocampus via the medial perforant path (mPP). Non-spatial information and information on color or shape, which are processed in the occipital and temporal cortices, respectively, enter into layer II of the lateral EC (LEC) and flow to the hippocampus *via* the lateral perforant path (lPP) (Fig. 1). Then the output signal of the hippocampus returns to layer II of the EC (ECII) through layer V of the EC (ECV). Thus, the connection between the EC and hippocampus is recurrent [4]. This recurrent neuronal network (EC-hippocampus-EC, etc.) is called the EC-hippocampus loop.

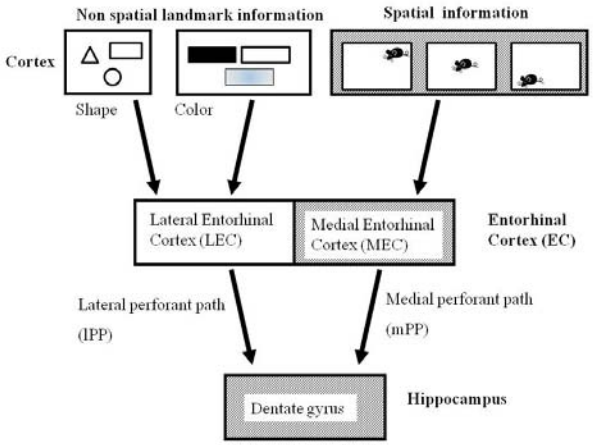

Fig. 1. Spatial information and non-spatial information flow in a brain. The signals on the spatial information first enter the medial entorhinal cortex (MEC) and are conveyed to the dentate gyrus (DG) of the hippocampus. Signals on non-spatial information enter the lateral entorhinal cortex (LEC) and are also conveyed to the dentate gyrus.

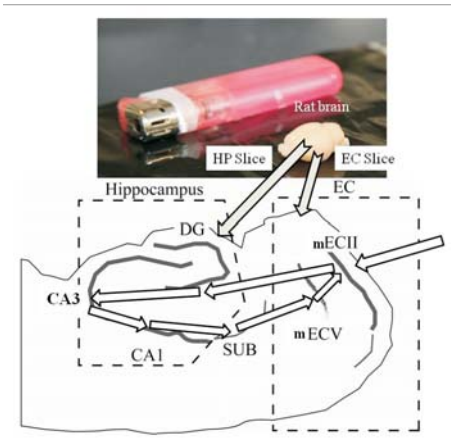

Fig. 2. The neuronal network between the entorhinal cortex and hippocampus is recurrent. A cross section including hippocampus and EC in the lower figure is shown in the upper picture. You can see the size of the rat brain compared

with a lighter. mECII, layer II of the MEC; SUB, subiculum. The subiculum is the gateway from hippocampus to the EC in the EC-hippocampus loop. mECV stands for layer V of the mEC. The arrows indicate the signal flow in the EC-hippocampus loop in the lower figure.

In memory processes in the brain, the synapses, i.e., the junctions between two neurons, undergo two kinds of change in the neuronal network [5]. One is a long-term potentiation, LTP, and the other is a long-term depression, LTD. In the LTP, the signal easily passes through the synapse, while in the LTD, it is difficult for the signal to pass through. In the learning process, both LTP and LTD occur, and it is thought that their occurrence forms a spatial pattern. These synaptic changes are controlled by the precise timing of the pre- and the postsynaptic spikes [6]. The resulting long-lasting synaptic change in spike-timing-dependent plasticity (STDP) is expressed as a function of the spike timing Δt between pre- and postsynaptic firing. In most systems studied to date, a presynaptic neuronal spike before the postsynaptic neuronal spike leads to LTP while a postsynaptic neuronal spike before the presynaptic neuronal spike leads to LTD [6]. Cases in which a presynaptic spike before a postsynaptic spike actually leads to LTD while the opposite timing leads to LTP, have also been observed [7]. These STDP rules have an asymmetrical function. There is also a symmetrical STDP function in which the synchronous firing of pre- and postsynaptic neurons leads to LTP while a shift of the timing results in LTD. The STDP rules are used in sequence learning [8] and the control of synchronous activity of neuronal oscillation [9]. In the research of the neural networks, Hebb's rule is ordinarily used as a learning rule. This rule has no temporal information, while the STDP rule does. When the neural network adopts the STDP rule as a learning rule, the network can use the temporal information of the neuronal spike more effectively. Igarashi and his collaborators including one of the coauthors of the present paper have proposed a model in which the EC-hippocampus loop and the STDP phenomena at the recurrent synapse of ECII are used for sequence learning in the brain [10]. In the model it takes a few tens of msec for the signal to propagate along the loop. When the first signal comes into the loop, the signal can be associated with the next signal, which has a delay around a few tens of msec according to the STDP rule at the recurrent synapses in ECII. Their model adopted a symmetrical STDP function. But the function at the synapse has not yet been clarified by a neurophysiological experiment.

The dentate gyrus (DG) of the hippocampus receives a signal from the EC via the medial perforant path (mPP) and lateral perforant path (lPP) in the EC-hippocampus loop. When a rat runs through a course of objects, the mPP conveys the spatial information of the objects, and the lPP conveys their non-spatial features (Fig. 1). The DG integrates the two kinds of information. To clarify how the DG integrates the information, the characteristics of the STDP function at the synapses of mPP and lPP must be studied. The STDP function at the synapse between the lPP and granule cells in the DG has already been measured experimentally [11]. It is symmetrical in shape. But the STDP function at the synapse between the mPP and granule cells has not yet been clarified.

In the present study, we explored the STDP rules at the synapse between ECII and ECV neurons and at the mPP synapse of the DG in the hippocampus.

2. Materials and Methods

Experiments were carried out in compliance with the Guide for the Care and Use of Laboratory Animals at the Graduate School of Life Science and Systems Engineering of Kyushu Institute of Technology. The STDP rule at the ECII synapse was recorded in an EC slice cut from a rat brain as shown in Fig. 2. The STDP rule at the DG synapse was recorded in a hippocampal slice cut from a brain as shown in Fig. 2. Rats were anaesthetized and decapitated, and the brains were removed. Then the slices were cut from the brains using a microslicer. Fifty-nine slices (450 μm thick) of the EC and hippocampus were prepared from twenty-six 3- to 4-week-old Wistar rats. They were transferred to each recording chamber, and perfused with oxygenated artificial nutrition solution. In the STDP experiment at the synapse of the ECII, a recording electrode was placed in the ECII cell layer to record the field excitatory postsynaptic potential (fEPSP) (Fig. 3). The fEPSP indicates the synaptic transmission at the synapse. One of the two stimulation electrodes was placed in the axon layer to stimulate the axons of the presynaptic neurons, and the other electrode was placed in the cell layer to stimulate the postsynaptic neurons of mEC (Fig. 3a). The electrode did not stimulate just one axon or neuron but several. In the experiment at the DG synapse in the hippocampus (Fig. 4), the recording electrode was put into the cell layer of the DG, and the two stimulation electrodes were located to stimulate the presynaptic and postsynaptic neurons. The stimulation protocols were the same in the EC and hippocampus (Fig. 3). The baseline response induced by the baseline stimulus was first recorded; then the paired stimulus at both the presynaptic and postsynaptic neurons was given to induce STDP at the synapse, and the baseline stimulus was given again to check whether the STDP was induced or not. The degree of stimulation at the baseline was adjusted so that the amplitude of fEPSP was 50 % of the maximum so that changes in fEPSP could be easily observed. The stimulus in the paired stimulus was adjusted to the minimum strength at which the postsynaptic neuron induced the spike. Twenty baseline stimuli were fed at intervals of 30 sec and the baseline responses of fEPSP were recorded. After the baseline stimuli, 120 paired stimuli were fed at intervals of 5 sec for the pairing process. In the pairing, the timing of the stimulation to the presynaptic and postsynaptic neurons shifted. After the pairing the baseline responses were again recorded for an hour at the same interval as before (Fig. 3b). The regression line of fEPSP at the latencies between 4 – 8 msec after the stimulation (Fig. 3b arrow) was extrapolated, and the slope of the line was calculated. It was used as an indication of the synaptic strength. To check whether LTP or LTD was induced, the averaged slope of fEPSP 10 min before the pairing was compared with that between 50 and 60 min after the pairing. The statistical test (student's t-test) was performed and the data with a significant difference

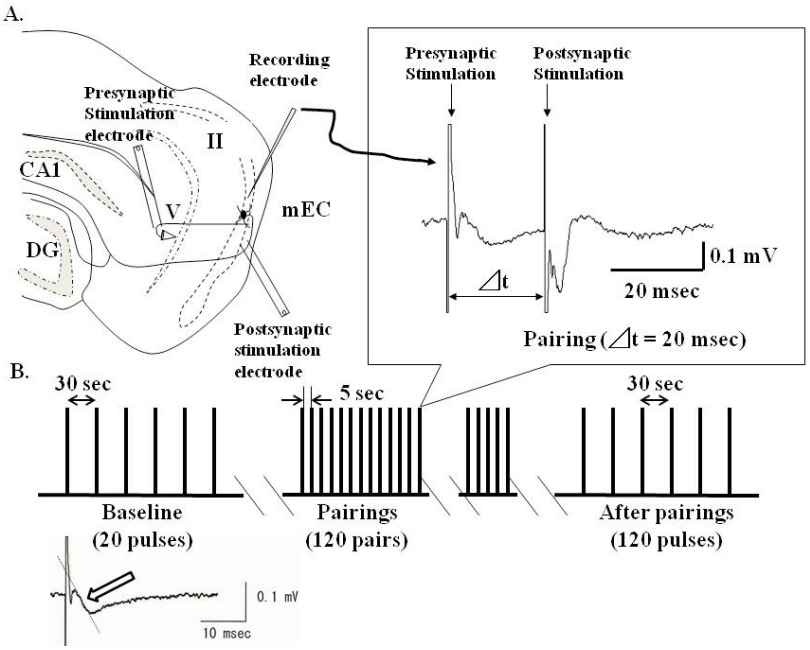

Fig. 3. The recording protocol for the STDP function at the ECII synapse. A. Sites where the recording and the stimulation electrodes were located. In the right inset, an example of the electrical signal from the recording electrode is shown. The x and y axes indicate the time and the field potential, respectively. B. The stimulation protocol to record STDP phenomena is shown. The vertical bars indicate the stimulations. The x-axis indicates the time. The inset shows the typical fEPSP. The arrow indicates the time when the slope of fEPSP is calculated. An extrapolated line is also shown.

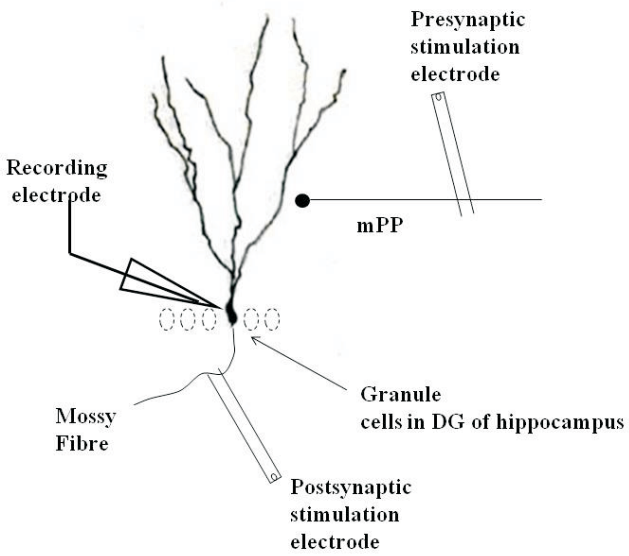

Fig. 4. Schematic diagram of the recording of the STDP function in the DG of the hippocampus.

($p < 0.05$) were adopted.

At the STDP rule, a positive spike timing ($\Delta t > 0$) indicates that the presynaptic neurons were stimulated first, and then the postsynaptic neurons were stimulated. Negative timing ($\Delta t < 0$) indicates the opposite. The synaptic change was recorded at spike timings from -60 to 60 msec at the ECII synapse, and from -40 to 20 msec at the DG synapse of the hippocampus.

3. Results

3.1. STDP function at the synapse of ECII

In EC slices, after the pairing of the positive timing of $\Delta t = 20$ msec, fEPSP was suppressed and the suppression lasted for at least 60 min (Fig. 5). The fEPSP slope was significantly decreased compared with the baseline slope before the pairing (significance probability $p < 0.01$). Therefore, LTD was induced (Fig. 5). On the other hand, the pairing at $\Delta t = 0$ msec induced the potentiation of fEPSP and lasted for an hour. The pairing induced LTP (Fig. 6).

STDP function at the synapse of ECII (Fig. 7) shows that at the spike timing Δt between the presynaptic and postsynaptic cells around 0-msec LTP was induced, while at the shifted timing between them around 20-msec LTD was induced. The shape of the STDP function was asymmetrical. This type of STDP function was first found at the distal synapse of the pyramidal cells in the cortex [12].

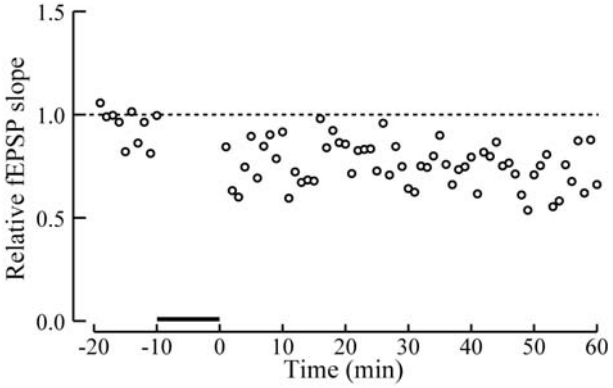

Fig. 5. LTD induced by the pairing of the positive spike timing Δt = 20 msec at the ECII recurrent synapse. The x-axis indicates the time, and the y axis indicates the relative fEPSP slope. The relative fEPSP slope is defined by the ratio of the fEPSP slope to the average for ten minutes before the pairing. The time zero indicates the end of the pairing. The horizontal thick bar indicates the pairing.

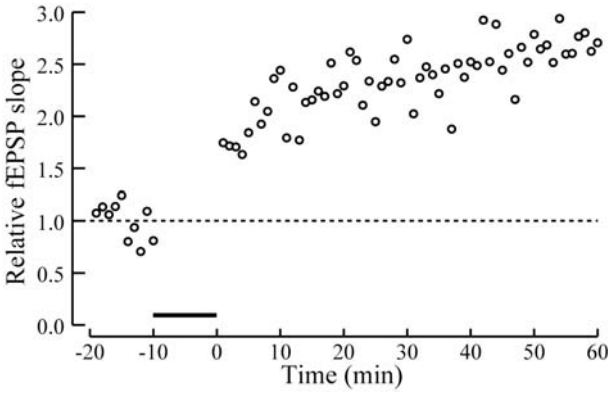

Fig. 6. LTP induced by the pairing.

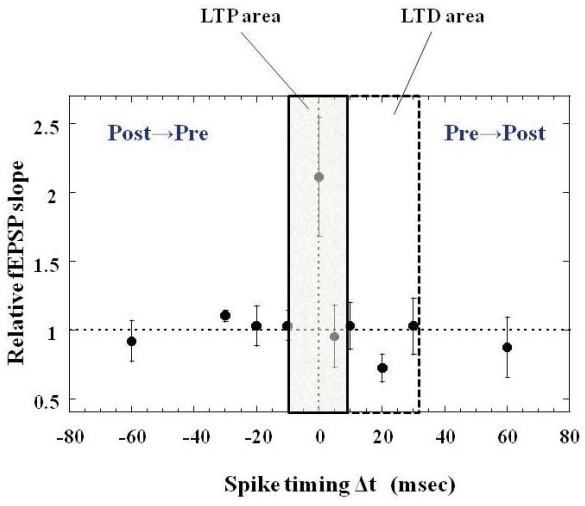

Fig. 7. STDP function at the ECII recurrent synapse. The filled circles and bars indicate the relative fEPSP slope and the standard errors of the means (SEM). The x-axis shows the spike timing, and the y-axis indicates the relative fEPSP slope. These data are obtained from forty slices of twenty male rats.

3.2. STDP function in dentate gyrus (DG) of hippocampus

In hippocampal slices, after pairing at the positive timing of Δt = 5 msec, LTP was slightly induced (Fig. 8), while the pairings at the negative timing of Δt = -10 msec induced LTD (Fig. 9).

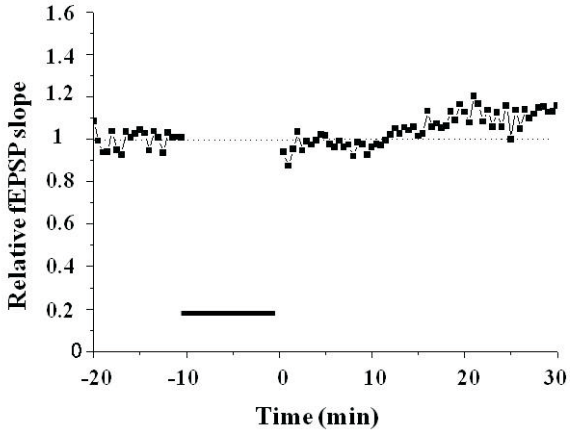

Fig. 8. LTP induced by the pairing of the positive timing Δt = 5 msec at the synapse in the DG of the hippocampus.

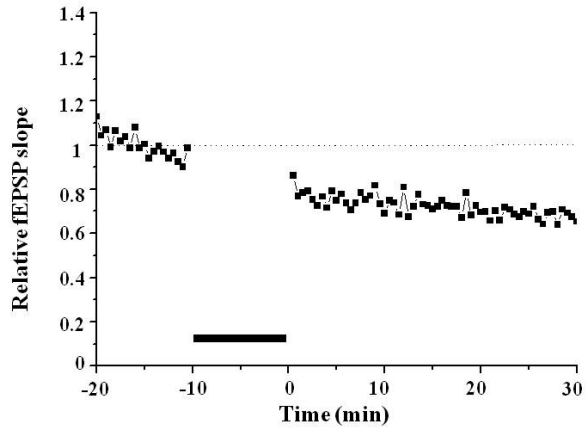

Fig. 9. LTD induced by the pairing of the negative timing Δt = -10 msec at the synapse in the DG of the hippocampus. The pairing suppressed the transmission.

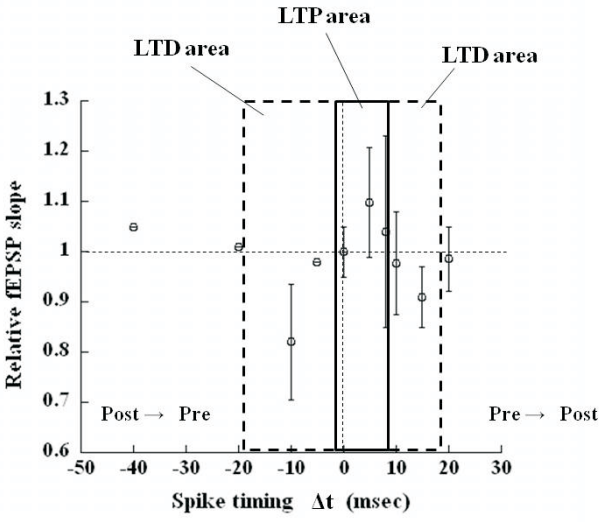

Fig. 10. STDP function at the synapse in the DG of the hippocampus. Circles and bars indicate the relative fEPSP slope and SEM. These data are obtained from nineteen slices of six male rats.

The STDP function at the DG synapse of hippocampus (Fig. 10) shows that at the spike timing between the pre-

synaptic and postsynaptic neurons around 5 msec LTP was induced, while when Δt is between 10 and 18 msec, and between -20 and -1 msec, LTD was induced. The shape of the STDP function is almost symmetrical, unlike the function at the ECII synapse.

4. Discussion

At the synapse of ECII, the STDP function was asymmetrical (Fig. 7). It had an LTP region around $\Delta t = 0$ msec, and had an LTD region at $\Delta t > 0$ msec. On the other hand, at the synapse of DG in the hippocampus, it was symmetrical (Fig. 10). It had an LTP region around Δt=5 msec, and had two LTD regions at $\Delta t < 0$ and Δt = -15 msec on both sides of the LTP region. These results suggest that the STDP function is different in different brain regions [13]. It is thought that induction of LTP or LTD depends on the rise in intracellular Ca^{2+} concentration at the postsynaptic neuron ($[Ca^{2+}]i$) by the pairing [14]. When $[Ca^{2+}]i$ increases so little by the pairing, the synapse does not change. When it increases moderately, LTD is induced. $[Ca^{2+}]i$ is increased by the neuronal spike. When the increase in $[Ca^{2+}]i$ is great, LTP is induced. Therefore, when the presynaptic and postsynaptic neurons fire simultaneously (Figs. 7 and 10), $[Ca^{2+}]i$ increases greatly in the postsynaptic neurons, and LTP is induced at both the EC and hippocampus synapse (Figs. 7 and 10). The spike timing between the postsynaptic and presynaptic neurons shifts, $[Ca^{2+}]i$ does not increase so much by the stimulation, and LTD is induced at the DG synapse of the hippocampus (Fig. 10). Only this mechanism does not explain the finding that there was no LTD region in the STDP function of the ECII synapse. The present asymmetrical STDP function found at the ECII synapse is a novel type. A similar asymmetrical STDP function was found at the remote synapse from the soma of the pyramidal neurons located in the neocortex of the brain [12], while the function mainly had an LTP region at the negative timing different from the present function. The mechanism of the function has not yet been clarified. There are feedback inhibitory neurons in the ECII network. The neurons may contribute to the STDP function.

In an open field with landmarks, a rat runs watching the landmarks. The rat memorizes the time-series of the position of the landmarks and associates their positions and features. From this information the rat recognizes its position. As a result, place cells emerge in the hippocampus [15]. The place cell in the hippocampus fires in the respective place field whenever the rat runs into the field from any direction. As a result, the hippocampus of the rat memorizes its position in the environment.

The granule cells in the DG of the hippocampus receive information from the EC *via* the mPP and lPP. The mPP conveys the spatial (positional) information of the landmarks and the lPP conveys information about their features. The mPP and lPP come from the mECII and lECII, respectively. The two signals converge in granule cells of the DG in the hippocampus. The granule cells in the DG of the hippocampus integrate these two signals (Fig. 1). The STDP function at the DG synapse with mPP (Fig. 10) and lPP in the hippocampus was asymmetrical [11]. It has an LTP area near $\Delta t = 0$ msec, and there are two LTD areas with negative and positive timing. When the granule cells fire simultaneously with the firing of mPP or lPP, the synapse of mPP and lPP on the granule cells is long-term potentiated. Therefore, there is a possibility that the granule cells will associate the non-spatial information of the landmark brought by the lPP with their positional information conveyed by the mPP when the two inputs arrive at the granule cells simultaneously. The hippocampus associates the features of the landmark objects with their positional information. The DG neurons, which associate the position and the features of the landmarks, can be regarded as place cells.

Igarashi *et al.* [10] has proposed a model of the brain by which the EC-hippocampus loop processes sequence learning of sensory inputs. In rats, sensory information to the EC is coded by the spike train. It is assumed that the frequency of the spike train is dependent on the distance between the rat and the landmark. When the rat is far from the landmark, the frequency of the spike train is low, for example, 30 Hz, and when the rat comes closer to the landmark, its frequency increases, say, to 40 Hz. The stellate cells in the ECII connect with each other *via* the recurrent neuronal network through the hippocampus (Fig. 2). Thus, the output of the stellate cells in the EC returns to the other stellate cells in the mEC with some delay. Igarashi's model has found that when two stellate cells acquire the inputs of spike trains of 40 Hz and 30 Hz, respectively, LTP is induced at the synapse from a 40 Hz-firing stellate cell to a 30 Hz-firing stellate cell according to the STDP rule [10]. Thus, when the rat is running through the landmarks A, B and C, the EC-hippocampus loop memorizes the sequence of the landmarks A, B, and C. Igarashi *et al.* [10] used the STDP function with the symmetrical Mexican hat type shape. One of the present coauthors, Hayashi, has shown that when EC stellate cells receive sensory inputs which contain the background noise, the asymmetrical STDP function with an LTD area for the negative timing and LTP area for the positive timing induces irrelevant synaptic enhancement at the ECII synapse [16]. Thus, they suggest that the LTD area at the positive timing of the symmetrical STDP function prevents the irrelevant synaptic change and enables robust sequence learning for sensory inputs containing the background noise. The STDP function found in the present paper has an LTD area at the positive timing. Using the function, the EC-hippocampus loop could process the sensory input signal with background noise more robustly.

Actually there are two loops, a mEC-mPP-hippocampus loop, which processes the time-series of the position, and a lEC-lPP-hippocampus loop, which processes the time-series of the features separately and in parallel. The time-series of the position of the landmark and the features of the landmarks are processed in the EC-hippocampus loop in parallel, and the position and features of the landmark are integrated and bound in the granule cells of the DG in the hippocampus. The parallel processing of the feature of the objects and the integration or binding of them may be the characteristics of the information processing of a brain system based on EC-hippocampus loop. In results, the system can interpret the environment around it freely, and it can adjust to its environment.

In brain-inspired systems, a new concept for studies linking the fields of brain science and engineering, it is thought that the results from brain science can be applied to engineering technologies [17]. The present work suggests the EC-hippocampus loop processes sequence learning based on features and positioning of landmarks, and the hippocampus integrates or binds the features and the positions in parallel. Using these processes a brain may navigate a path of movement. The proposed brain sequence-learning model using the EC-hippocampus loop may be applicable to the sequential learning of landmarks by a mobile robot. A navigational system for a robot based on the present results can be developed.

Our results suggest that there is the possibility for a brain to use a recurrent neuronal network and asymmetrical STDP function to achieve sequential learning. This processing has a feed-forward character. On the other hand, recurrent neural networks in the engineering field usually adopt an algorithm of back propagation through time (BPTT) to learn the sequence of the time-series signal [18]. If the algorithm were used in a brain, some neurons could fire retrospectively. Actually, the hippocampal neurons replay in reverse [19]. Which algorithm the brain adopts must be determined in the future studies. In addition, which algorithm is useful for a robot to navigate a path of moving will be clarified by the studies of the brain-inspired systems.

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