Neural network organization of the spatial map

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研究成果の概要（和文）：海馬は、空間ナビゲーションとともに、エピソード記憶にも重要な役割を果たしている。 最初期遺伝子であるZif268の発現を神経活動の指標として用いて行った我々の以前の研究では、空間記憶学習中の動物において、Zif268陽性細胞はクラスターを形成していることが明らかとなっている。本研究では、連続的嗅覚刺激弁別学習や文脈的恐怖条件づけなどのエピソード記憶課題においても、海馬のCA1/CA3領域にクラスター状に分布するZif268陽性細胞が見られることを新たに見出した。以上のことから、海馬には様々な情報のエンコードの神経基盤となる機能的構築が見られるを結論された。

研究成果の概要（英文）：The hippocampus is essential for spatial navigation as well as episodic memory. Using immediate early genes (Zif268), we previously found that in animals engaged in a spatial task, Zif268 immunoreactive (IR) cells in the hippocampus were grouped in clusters. Here, we investigated whether a similar organization exists to encode for episodic memory. We found that animals performing a sequential odor discrimination task, pyramidal cells in the CA1/CA3 fields formed Zif268 IR clusters. In a second study, we tested animals in contextual fear memory. We found that hippocampal neurons were recruited in both spatial and episodic memory. These findings confirm that there is a fundamental functional organization in the hippocampus to encode all types of information. In a third study (not yet completed), we will be using optogenetic methods to inhibit/activate the major afferents to the hippocampus arising from the medial and lateral entorhinal cortex to confirm the validity of the clusters.

研究分野：　Behavioral Neuroscience

キーワード：　hippocampus　memory　place cells　episodic memory　immediate early genes

１．研究開始当初の背景

Based on the discovery of 'place cells' (O'Keefe and Dostrovsky, 1971) the hippocampus is thought to function as a cognitive or spatial map (O'Keefe and Nadel, 1978). In the ensuing five decades many of the components (e.g., grid cells, head direction cells, etc) of the navigational system have been described. (O'Keefe, Moser and Moser received the 2014 Nobel Prize in Physiology or Medicine for the discovery of spatial navigation system in the brain.) Yet, the functional configuration of the spatial map remains a complete mystery - mainly due to limitations of simultaneous unit recordings (usually less than 100 units). Based on recording studies, the spatial map is thought to be non-topographically (randomly) organized, since place cells do not necessarily have adjacent place fields. We believe this to be wrong, mainly due to the limitation of the unit recording method which would not render it possible to construct the spatial map in the brain. In previous studies we used immediate-early genes (Zif268, Homer1) to map neuronal activity in animals engaged in a spatial task and found a topographic organization in the dorsal hippocampus, comprised of repetitive neuronal clusters of a few active cells spread (approximately 200-400µm apart) across the CA1 and CA3 hippocampal fields (Nakamura, et al., 2010; Pavlides, et al., under revision). We believe that these findings could, for the first time, provide great insight into how the spatial map may be organized.

Besides spatial navigation, the hippocampus plays a major role in episodic (discrete events) memory. This has been documented in numerous studies. For example, both lesion (Kesner and Novak, 1982; Fortin et al., 2002) and unit recording (Wood et al., 1999) studies have reported that the hippocampus is required for sequential memory. Another task that the hippocampus is critically involved in is contextual fear memory (Ledoux, 1998). There have been very few studies aimed at examining functional neuronal organization in the hippocampus for episodic memory. For the proposed studies we hypothesized that a basic functional organization must exist in the hippocampus for all types of information processing and that it is probably a cluster-type organization.

２．研究の目的

The first objective of the proposed studies was to determine possible functional neuronal organization in the hippocampus for episodic memory. For this we used a sequential order, odor discrimination task, for which the hippocampus is involved in. Given the prolonged (more than a month) training for the animals to achieve criterion, we conducted a second set of experiments using contextual fear conditioning. A second objective of the proposal was to determine whether the same set of cells/clusters encode for both spatial and episodic memories. A final objective was to validate the clusters we observed in the hippocampus by inhibiting the main inputs arising from the MEC and LEC to determine effects on hippocampal clusters.

３．研究の方法

For the first aim, we trained animals in a sequential order, odor discrimination task. Animals were presented with a sequence of odors and 20sec later they were presented with two odors and were required to choose the odor that came earlier in the sequence. Once they reached criterion of 80% correct, they were sacrificed and their brains processed for Zif268 immunohistochemistry to determine topographical organization of hippocampal neuronal activity. In a second study, we contextual fear conditioned animals, tested them 24h later for fear memory, and performed a similar procedure as previous study to determine topographic cellular organization in the hippocampus. For the third specific aim, we have acquired an optogenic setup and are in the process of optimizing and conducting experiments to inhibit/stimulate afferents to the hippocampus from the MEC/LEC to determine effects on hippocampal clusters.

４．研究成果

In both the sequential order, odor discrimination as well as the contextual fear conditioning tasks we observed Zif268 IR clusters in the CA1 and CA3 of the hippocampus, similar to what we had previously observed for the spatial task (Fig. 1).

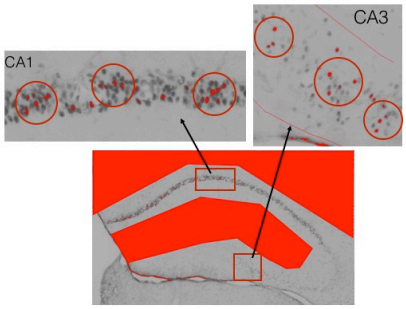

Fig. 1. Immunohistochemistry for Zif268 in the dorsal hippocampus in animals engaged in a sequential order, odor discrimination task. Zif268 IR clusters were observed in both the CA1 and CA3 hippocampal fields.

However, there was a higher number of Zif268 IR cells and the number of clusters in the CA3 field of experimental in comparison to control animals (Fig. 2). We are in the process of

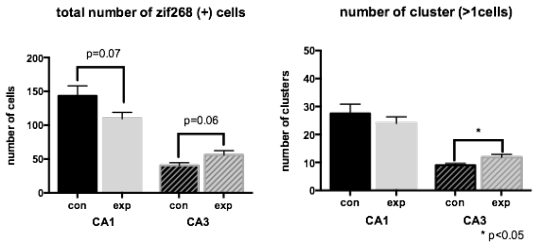

Fig. 2. Average number of Zif268 IR cells and cell clusters in the CA1 and CA3 hippocampal fields. There was a higher number of Zif268 IR cells and clusters in the CA3 than the CA1 of experimental in comparison to control animals.

completing a manuscript to be submitted for publication. A similar type of cluster organization was also observed in the hippocampus in animals trained in a contextual fear conditioning task (Fig. 3). We are in the process of optimizing the optogenetic setup and starting experiments proposed for specific aim 3 (Fig. 4). We do not have sufficient results for this study yet.

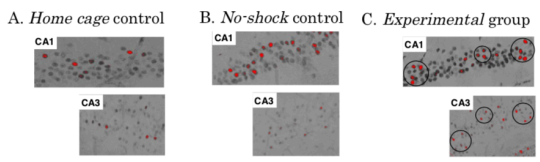

Fig. 3. Distribution of Zif268 IR cells in the dorsal hippocampus in fear conditioned (Experimental) and control groups. A cluster-type organization was observed in both the CA1 and CA3 fields.

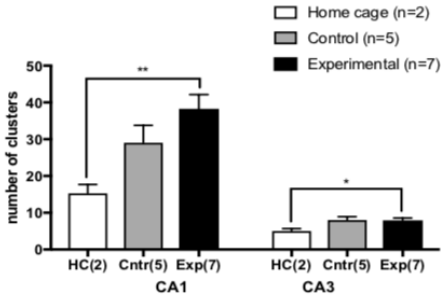

Fig. 4. Average number of Zif268 IR cells in contextual fear conditioned and control groups. A higher number of Zif268 IR cells were observed in both the CA1 and CA3 hippocampal fields.

５．主な発表論文等
（研究代表者、研究分担者及び連携研究者には下線）

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６．研究組織

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