Neuroscience Research 129 (2018) 17–23

Contents lists available at ScienceDirect

Neuroscience Research

journal homepage: www.elsevier.com/locate/neures

Review article

Social memory engram in the hippocampus

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ARTICLE INFO

Article history:
Received 27 March 2017
Received in revised form 21 May 2017
Accepted 25 May 2017
Available online 1 June 2017

Keywords:
Social memory
Hippocampus
Engram
vCA1
dCA2
Avpr1b
Grandmother cell theory

ABSTRACT

Social memory is one of the crucial components of episodic memories. Gregarious animals living in societies utilize social memory to exhibit the appropriate social behaviors such as aggression, avoidance, cooperative behavior, and even mating behavior. However, the neural mechanisms underlying social memory in the hippocampus remains mysterious. Here, I review some evidence from work done in rodents and primates on the brain region(s) and circuits encoding and/or retrieving social memory, as well as a storage for social memory (i.e. social memory engram neurons). Based on our recent findings that neural ensemble in ventral CA1 sub-region of the hippocampus possesses social memory engram, I would discuss the neural network for social information processing in order to encode social memory; and its evolutionary conservation between rodents and human.

Contents

1. Introduction

For gregarious animals that live in societies or groups, it is crucial to remember and recognize different conspecific individuals (i.e. having social memory) in order to exhibit the appropriate social behavior such as aggression, avoidance, cooperative behavior, and even mating behavior.

As an example, social defeat drives one of the behavioral adaptive responses that requires the utilization of social memory observed in mice. It is a result of repeated exposure to more aggressive members of the same species (termed as the "social defeat conditioning paradigm"). When that memory of having been defeated is entrenched and remains salient, the adaptation is achieved with a behavioral readout characterized by the animal's social avoidance strategy specifically towards its aggressors (Berton et al., 2006; Franklin et al., 2017). This adaptation is supposedly beneficial for the animal in protecting its well-being, whilst facilitating alternative routes to essential resources for survival (Price and Sloman, 1984).

On the other hand, other species such as the prairie voles and medaka fishes form highly organized societies; and utilize social memory mainly for their female sexual preference behaviors. Female sexual preference was proposed by Charles Darwin in "The Descent of Man, and Selection in Relation to Sex" (Darwin, 1871) wherein females tend to mate with selected males by species-specific criteria. Interestingly, behavioral characteristics such as the "social familiarity", apart from morphological features, can be subjected to females' sexual selection in a mate. The prairie

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https://doi.org/10.1016/j.neures.2017.05.007
0168-0102/

vole is well known as a socially monogamous animal that forms enduring social bonds with their respective mates, and displays bi-parental behavior (McGraw and Young, 2010). In a partner preference behavioral test using the prairie vole, a test vole tends to spend more time interacting with its mating partner (Williams et al., 1992). Similarly, the female medaka fish, being equally capable of remembering conspecific males, shows preference to mate with a familiar male (Okuyama et al., 2014). Social familiarization facilitates a pacemaker potential recorded in terminal-nerve gonadotropin releasing hormone3 (TN-GnRH3) neurons, and has shown enhanced female mating acceptance specifically toward a familiar male (Okuyama et al., 2014). In order to mate with females and increase their fitness, the male medaka fishes struggle to remain as close to the females as they can (Yokoi et al., 2015). Doing so will increase their odds of being selected by the females along with the right to mate (Yokoi et al., 2016).

We can classify social defeat and female sexual preference observed in the prairie vole and medaka fish as behaviors in which social memory is associated with negative and positive valence respectively. In other words, encoding and retrieving social memory provide crucial information to elicit the subsequent appropriate behavior response. However, the mechanism underlying social memory itself remains largely unclear. This review will focus on the neural mechanisms of social memory, and attempt to elucidate how social memory is encoded and stored via the hippocampal neurons.

2. Social memory in the human hippocampus

Evidence from animal studies and human patient studies have demonstrated a key role of the medial temporal lobe (MTL) and the hippocampus in the acquisition of episodic memories, their consolidation and recall (Andersen, 2007). Episodic memories include several components such as spatial information (Where), temporal information (When), event information (What), and social information (Who) (Allen and Fortin, 2013; Hitti and Siegelbaum, 2014; Kitamura, 2017; Squire and Wixted, 2011), suggesting that social memory is, at least in part, stored in the hippocampus. Indeed, human patients with hippocampal or MTL lesion exhibit multiple memory deficits including an impaired social memory. For instance, using famous faces test, H.M. performed marginally better than other participants on faces from the 1920s and 1930s (before injury), but was significantly worse in performance on faces from the 1950s (after injury) onwards (Corkin, 2002). Smith et al. examined face recognition memory in patients with hippocampal lesions; and found that memory for faces remains intact after hippocampal lesions if the testing occurs immediately after the encoding phase. However, that memory is impaired for the participants when the interval between encoding and testing exceeds 15 min (Smith et al., 2014). These evidences suggest that the hippocampus is required for encoding and/or retrieving social memory.

Based on the fact that the hippocampal lesion patients can distinguish individual faces without an interval between learning the faces and the testing phase (Mundy et al., 2013; Smith et al., 2014), we can conclude that the hippocampus is dispensable for face perception itself; because face perception is said to be organized by specialized face-patch neurons for the human face-processing system (Tsao et al., 2003; Tsao et al., 2008). Using functional magnetic resonance imaging (fMRI), the face-patch neurons are identified in the temporal lobe, including the fusiform face area, the occipital face area, and a face area in the superior temporal sulcus (Haxby et al., 2000; Kanwisher et al., 1997). Dysfunction of the face recognition in the fusiform cortex results in face blindness (also called Prosopagnosia) (Hadjikhani and de Gelder, 2002): a cognitive disorder of face perception in which the ability to recognize familiar faces, including one's own face, is impaired (Sergent and Poncet, 1990). The hippocampus simply obtains the relevant social information, such as face information processed by other cortical regions, and stores it. The next chapter reviews some physiological characteristics of human hippocampal neurons in terms of their reactivity towards social cues.

3. Grandmother cell theory and "Jennifer Aniston" neuron

Itzhak Fried, Quian Quiroga, and their colleagues did pioneer studies on the potential capability of single human hippocampal neurons to store a certain "concept". Using electrode recordings of the human brain, Fried revealed that single neurons in the MTL discriminated human faces from objects (Fried et al., 1997). Next, they attempted to figure out the characteristics or attributes of visual stimuli that will activate single hippocampal neurons by trying out categorical pictures such as emotional faces, face drawings, famous faces, objects, spaces, cars, foods, animals, and patterns. Subsequently, they show that a certain degree (14% of recorded neurons) of a single category-selective hippocampal neurons firing in a distinct manner when presented with the respective stimuli. In other words, there is basically segregation of categories at level of single hippocampus neurons (Kreiman et al., 2000).

Work by Quiroga et al. (2005) reveals that a remarkable number of human hippocampal neurons are selectively activated by strikingly different pictures of particular persons (Fig. 1). For example, a single neuron located in the right anterior hippocampus is selectively activated by only pictures of Halle Berry (the actress). Interestingly, this single neuron is also activated by several pictures of Halle Berry dressed as "Catwoman" that is her character in a movie film, but not by other images of "Catwoman" played by other actresses. Not only that, the neuron is also activated when presented a stimulus of the written string "Halle Berry" (Quiroga et al., 2005). These evidence demonstrated that the hippocampal neurons possess the capability to respond with multimodal sensory input including visual and auditory cues; thereby driving social memory recall of a specific individual (Quiroga et al., 2009). Those single hippocampal neurons are reactivated even by "free recall" of social memory (Gelbard-Sagiv et al., 2008). They classify those neurons, that selectively respond to specific individuals like Jennifer Aniston, as the "Jennifer Aniston neurons" – proposing the idea of "concept cells" in the MTL and their ability to store a single "concept" (Quiroga, 2012; Quiroga et al., 2005). The physiological characteristics of "concept cells" are different from those observed in face-patch neurons. One rationale behind the formation of "Jennifer Aniston neurons" could be that stimuli of well-known, familiar individuals are more likely to elicit selective responses in MTL neurons as compared to stimuli of unknown and/or unfamiliar individuals (Viskontas et al., 2009). Therefore, such neurons come into being as a consequence of the specific cues encoded and retrieved via social memory.

4. Social memory in rodents: CA2 and AVP

In the case of rodents, since mice and rats naturally tend to spend more time interacting with a novel individual relative to a familiar one (social discrimination), the degree of social memory can be quantified by calculating the total interaction duration with novel and familiar mice respectively (Camats Perna and Engelmann, 2015). However, the literature as of date has not reached a consensus regarding the role of the hippocampus in social memory formation in this aspect. In rats, some early cytotoxic lesion studies concluded that the hippocampus is dispensable for recognizing a familiar conspecific (Bannerman et al., 2001; Squires et al., 2006). On the other hand, lesions of the medial septum, possessing strong

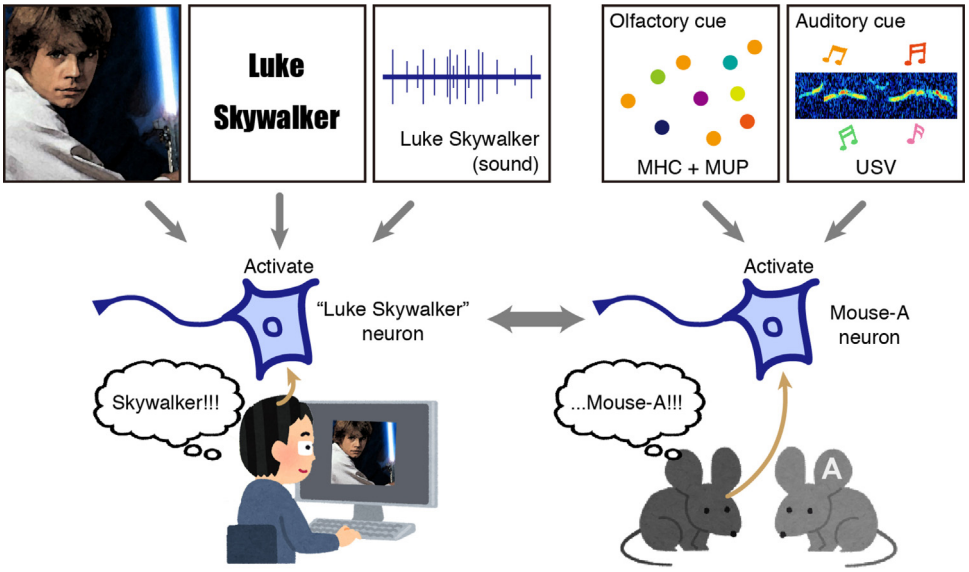

Fig. 1. Comparison between "Luke Skywalker neuron" in Grandmother cell theory and mouse-A neuron. Luke Skywalker neuron in our human brain is activated not only when viewing pictures of Luke Skywalker, but is also activated when reading a written string "Luke Skywalker", and upon hearing the verbalization of "Luke Skywalker" (Quiroga, 2012). In the case of rodents, olfactory cues (MHC class I protein and MUPs) and auditory cues (ultrasonic vocalization; USV) are utilized for representing social information. Mouse-A neurons in the hippocampus are activated upon retrieving mouse-A information.

reciprocal projections to and from the hippocampal formation (Fournier et al., 1993; Terranova et al., 1994) and fimbria, carrying a number of fiber projections both to and from the hippocampus (Maaswinkel et al., 1996), resulted in impaired social memory. In mice, Kogan et al. demonstrated that whole hippocampal lesion led to social memory impairment (Kogan et al., 2000).

A recent series of studies sought out an important role of the hippocampal CA2 sub-region, a small region between CA1 and CA3 (Kohara et al., 2014), expressing vasopressin 1b receptor (Avpr1b) for social memory function (Caruana et al., 2012; Dudek et al., 2016). Firstly, pharmacological studies revealed that subcutaneous injection of arginine vasopressin (AVP) prolongs social memory; whereas that of vasopressin receptor antagonist impairs it (Bluthe et al., 1993; Dantzer et al., 1987). Local injection of vasopressin receptor antagonist into the hippocampus also leads to a similar social memory impairment (van Wimersma Greidanus and Maigret, 1996).

The vasopressin 1b receptor (Avpr1b) is largely expressed in CA2 pyramidal neurons (Young et al., 2006), which is later confirmed by the Allen Brain Institute (Lein et al., 2005; Lein et al., 2007). Avpr1b knockout mice show significant impairment in social memory and social interaction motivation (DeVito et al., 2009; Wersinger et al., 2002; Wersinger et al., 2004). More importantly, a recent study had bolstered the AVP function in dorsal CA2 (dCA2) neurons by optogenetics (Smith et al., 2016). They used optogenetic activation to excite terminals of AVP expressing paraventricular nucleus (PVN) neurons in the dCA2 region of AVP-Cre transgenic mice. PVN-dCA2 circuit activation of AVP neurons markedly enhances social memory if the stimulation is performed during memory encoding, but not its retrieval. Since the activation effect is blocked by an Avpr1b antagonist, it is interpreted that AVP release by the optogenetic activation specifically into dCA2 region during encoding phase does enhance social memory. Additionally, Avpr1b knockout mice exhibit markedly reduced aggression (Wersinger et al., 2002); and this behavioral observation is supported by the evidence that Avpr1b selective antagonist injection leads to reduction of aggression behaviors in hamsters (Blanchard et al., 2005). The replacement of Avpr1b expression in the dCA2 region of Avpr1b knockout mice can rescue aggression levels to that of wild-type mice without altering anxiety-like behaviors (Pagani et al., 2015). Interestingly, another type of AVP receptor Avpr1a, whose expression is not restricted to CA2, is crucial for social memory as well; therefore suggesting AVP has a key role for enhancing social memory encoding in multiple brain regions (Bielsky et al., 2004; Ferguson et al., 2002; Winslow and Insel, 2004).

A more straightforward evidence that supports the role of dCA2 in social memory was reported by genetic inactivation of dCA2 pyramidal cells (Hitti and Siegelbaum, 2014). Tetanus toxin expressing adeno-associated virus (AAV) was injected into the dCA2 of Amigo2-Cre (CA2-Cre) transgenic mice; and it resulted in impairment of social memory without affecting other forms of hippocampal-dependent memory. Lesions in dCA2 region by site specific *N*-methyl-D-aspartate microinjection also resulted in impaired social memory (Stevenson and Caldwell, 2014). All in all, these are proof that dCA2 is indeed necessary for social memory.

5. vCA1 neurons storing social memory

In mining for the brain regions and neural circuits within the hippocampus that store social memory, we attempted to identify them via the presence of the social memory "engram". The memory "engram" (roughly equivalent to "memory trace"), which was first conceived by Richard Semon, is the theory that learning elicits persistent physical and/or chemical changes in specific neurons (i.e. "engram cells") that retain information and are subsequently reactivated upon appropriate retrieval conditions (Semon, 1911; Semon and Simon, 1921; Tonegawa et al., 2015a,b). Therefore, artificial or natural reactivation of engram cells by a part of the original stimuli delivered during learning results in memory recall (Tonegawa et al., 2015a).

Recently, we found that social engram neurons exist in ventral CA1 (vCA1) sub-region of the hippocampus (Okuyama et al., 2016). Optogenetic inhibition of the vCA1 pyramidal neurons, but not dorsal CA1 (dCA1) neurons, resulted in an impaired social discrimination ability observed in mice. This impaired social discrimination holds true during both the inhibition of encoding and retrieving

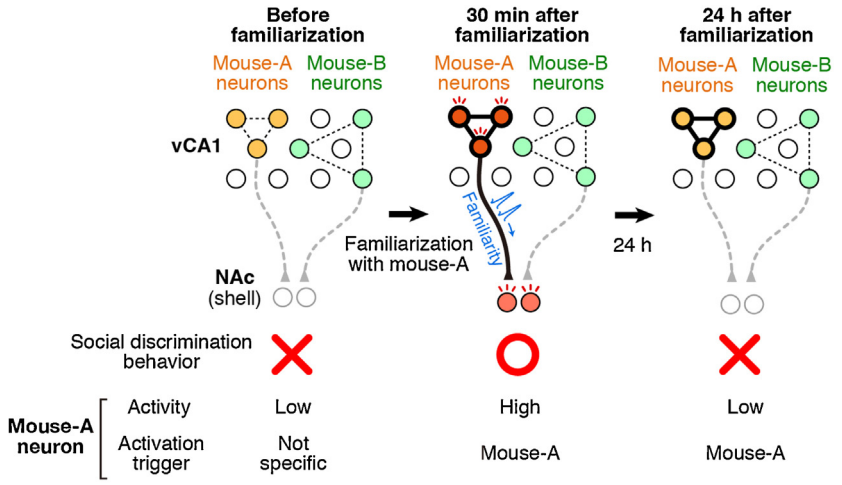

Fig. 2. Neural mechanism model for social memory and social discrimination behavior. Before familiarization, the memory is still non-existent; therefore Mouse-A neurons do not form. 30 min after familiarization, some neurons show high levels of activity, and are assigned as mouse-A neurons. Neural activity encoding social familiarity is conveyed to NAc shell to elicit social discrimination behavior. 24 h later, social discrimination behavior is not detected, and that correlates with the low activity of mouse-A neurons. However, Mouse-A neurons remain activated by social interaction with mouse-A specifically; suggesting that even if social memory is undetected by social discrimination test (SDT), the mouse-A ensemble partially remains. Modified figure from Fig. S19 of Okuyama et al., 2016.

phases of social memory. To prove the presence of social engram in the vCA1, we performed optogenetic activation of the vCA1 neural ensemble which responds to a specific mouse during social memory encoding. Even if the memory is lost after a long separation interval, the optogenetic activation of the vCA1 neural ensemble can fully restore that social memory. Additionally, the artificial association between the vCA1 neural ensemble encoding the memory of a specific individual with negative or positive unconditioned stimuli (e.g., foot-shock or cocaine injection) can elicit avoidance from or preference for the individual accordingly (also known as the "memory inception" experiment). The social memory engram neurons in vCA1 was shown to project to nucleus accumbens (NAc) shell; and neural activity of the vCA1-NAc is necessary and sufficient for eliciting the appropriate social discriminatory behavior. Taken together, vCA1 neurons and their NAc shell projections are components of the storage site for social memory (Fig. 2).

The vCA1 neural ensemble in the hippocampus, as well as presumably several other neurons upstream and downstream of the vCA1 neurons, are recruited to the encoding of an individual. For example, olfactory social cues in urine are detected by the main olfactory epithelium (MOE) and vomeronasal organ (VNO) in mice, and convey primary information about individuals for social memory (Brennan and Zufall, 2006; Dulac and Wagner, 2006; Leinders-Zufall et al., 2004; Spehr et al., 2006). A series of studies have revealed that the polygenic complexes of the major histocompatibility complex (MHC) (Overath et al., 2014; Singh et al., 1987) and the major urinary proteins (MUPs) (Hurst et al., 2001) have a large degree of variety among individuals (Cotton, 2007). Also, auditory social cues such as ultrasonic vocalization (USV) (Holy and Guo, 2005) convey information regarding male mice strains to females in order to discriminate among male song characteristics for female sexual preferences (Asaba et al., 2014a,b; Sugimoto et al., 2011). This combination of sensory cues plausibly forms a representative signature of each individual (Fig. 1). In other words, some ensembles of sensory neurons throughout a brain (e.g. MOE/VNO and auditory cortex) might be activated during the encoding phase to form the representation of a specific mouse. Besides those sensory neurons, neural ensembles in dCA2 and NAc are probably activated as well. In our recent review paper, we proposed the concept of an engram cell pathway – a set of engram cells for a given memory which are directly or indirectly connected by specific neuronal circuits (Tonegawa et al., 2015a). For social memory, we can assume that social information flows as follows; MOE/VNO-dCA2-vCA1-NAc (Fig. 3A), which includes a certain social memory engram or social memory engram pathway.

Do all of the aforementioned regions store social memory engram? Indeed, the association of upstream or downstream neurons with emotional valence might partially lead to avoidance or preference behavior to the specific mouse; as seen in the memory inception experiment using vCA1 social engram. To examine the persistent changes observed in engram neurons, we conducted *in vivo* physiological analysis by Schnitzer's microendoscope (Ziv et al., 2013). After encoding social memory, the proportion of activated vCA1 neurons which responds to the memorized mouse is shown to have increased. The strength and stability of neural activity observed in the social engram neurons are greater in response to the familiar mouse as compared to that towards a novel mouse (Okuyama et al., 2016). These experiments showed that firing properties with Ca^{2+} activity of vCA1 neurons has been modified following social memory encoding; and this correlates with successful memory recall. The collective results reinforced the idea that vCA1 is a storage site for social memory information.

6. Conclusion and future direction

This review focused on social memory a component of episodic memory in the hippocampus. Studies done on human participants revealed the physiological property of single hippocampal neurons, and proposes the idea of the "Grandmother cell" or "Jennifer Aniston neuron" theory. On the other hand, experiments using different animal models have allowed us to conduct neuronal cell type-, brain region-, and neural circuit- specific functional and physiological analyses. One important query is to question if the rodent vCA1 neurons, which we have identified as the familiar mouse-A neuron, are analogous to primate "Jennifer Aniston neurons" (Fig. 1).

One of most elusive questions in episodic memory is how the different types of information are integrated. For example, as mentioned in this review, multimodal sensory social cues such as olfactory, auditory, and probably visual cues are used for representation of social information to encode social memory for a specific individual. Along the hierarchy of memory formation, social memory (who) should be integrated with spatial mem-

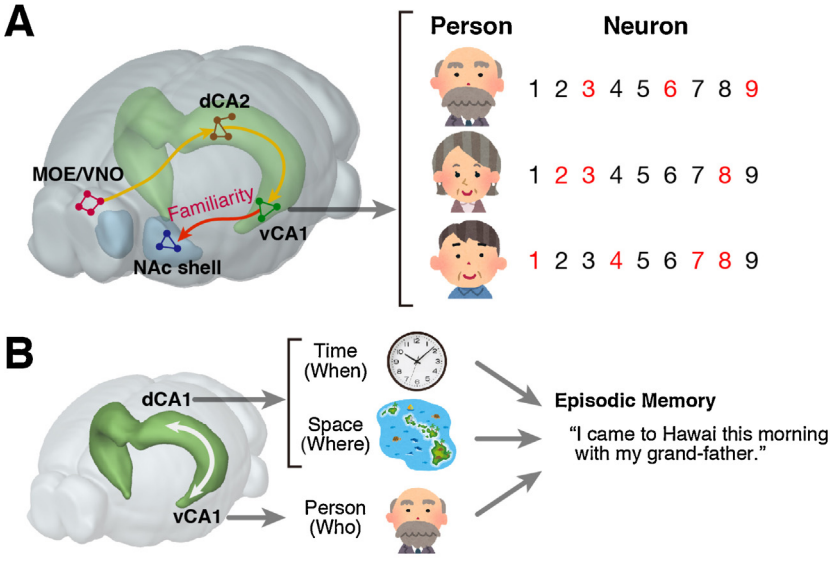

Fig. 3. (A) Model of social information flows including "social engram pathway" in rodents. Social information composed from multimodal sensory cues is conveyed from one neural ensemble to another in different brain regions repeatedly. The vCA1 neurons encode social memory in a population-coding manner. A specific set of neurons represents a specific individual. (B) Functional distribution for representing a complete piece of episodic memory. Spatial and temporal memories are encoded in dCA1, whereas social memory is encoded in vCA1.

ory (where) (Moser et al., 2008) and temporal memory (when) (Eichenbaum, 2014; MacDonald et al., 2011) for a complete piece of episodic memory. However, as of date, it remains largely unknown which neural circuits are responsible for the integration process and the underlying mechanisms. Physiological studies have revealed that spatial and temporal information are chiefly processed by the dorsal hippocampus of rodents (corresponding to posterior hippocampus of primates) (Fanselow and Dong, 2010; MacDonald et al., 2011). A rat recording study showed that no cells in dCA1 responded differentially to individuals; suggesting that social memory might not be encoded by dCA1 (von Heimendahl et al., 2012) at all. Supporting that argument, our study showed that the ventral hippocampus of rodents (corresponding to anterior hippocampus of primates) encodes social memory (Okuyama et al., 2016). This intrinsic pattern of connectivity in the hippocampus is fairly invariable along the longitudinal axis, and is conserved across many species (Andersen et al., 1971; Strange et al., 2014), suggesting that evolutionally conserved circuits to match up dorsal and ventral hippocampus pathway for describing a complete episodic memory composed of spatial, temporal, and social information (Fig. 3B). Of course, some of processes for sensory information and integration must be species specific (Tibbetts and Dale, 2007); because human basically utilize face recognition for social memory, whereas rodents employ olfaction and auditory sensory cues for that purpose. So which information processing is evolutionally conserved and which is not? Which brain region(s) and circuits regulate the integration process? While most fishes, including the medaka fish, do not have hippocampi, they are still capable of encoding social and spatial memories. What, then, is the purpose of having the hippocampus in higher-order organisms? Numerous unresolved questions still remain to this day in this exciting field of neuroscience.

Acknowledgements

I thank Drs. Susumu Tonegawa (MIT) and Hideaki Takeuchi (Okayama University) for constructive discussion; and Rosary Yuting Lim (MIT) for paper preparation. This research was supported by Grant-in-Aid for a Japan Society for Promotion of Science (JSPS) postdoctoral SPD fellowship (to T.O.) and Junior faculty developing program (to T.O.).

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