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Review article

Social memory engram in the hippocampus

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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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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