Hippocampus

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Definition

The hippocampus (from the Greek "seahorse") is a brain structure located in the medial temporal lobe that is primarily responsible for mapping spatial relations, temporal sequence information, and the formation of episodic memories.

Introduction

The hippocampus (from the Greek "seahorse") is a brain structure located in the medial temporal lobe that is primarily responsible for mapping spatial relations and the formation of episodic memories. The hippocampus is commonly described as being made up of the cornu ammonis (divided into sub regions CA1, CA2, CA3) and dentate gyrus. The "hippocampal formation" may also include the subiculum, parasubiculum, presubiculum, and entorhinal cortex (See Fig. 1). The hippocampus' main computational functions are thought to involve pattern separation, pattern completion, and distributing new memories to cortex via memory consolidation (McNaughton and Morris 1987). Spatial theories of hippocampal function argue that its neurons form an allocentric spatial map that tracks an animal's position and movement through space, allowing for the computation of online spatial relations like shortcuts. Theories of hippocampus suggest that it is central to relational or episodic memory that link together temporal, perceptual, spatial, and contextual information into unique events and common elements (Ergorul and Eichenbaum 2004).

Historical Developments

In 1547, the hippocampus was first described by Julius Caesar Aranzi, a Venetian anatomist who compared the shape of the structure to both a silk worm and a sea horse. Vicq d'Azyr made a distinction between the hippocampus major and minor (now identified as the calcar avis). In 1742, De Garengeot chose the term cornu ammonis (CA) to describe the region, which invoked the ancient Greek God Ammon (related to the Egyptian God Amun), who is often represented as possessing the horns of a ram (Falougy and Benuska 2006).

In the early days of evolutionary theory, surrounding the publication of Darwin's *On the Origin of Species*, there was a public debacle known as the Great Hippocampus Question. In 1857, Richard Owen suggested that the hippocampus minor (now classified as the calcar avis) was unique to humans, and that it was not present in monkeys. In 1858, Thomas Henry Huxley

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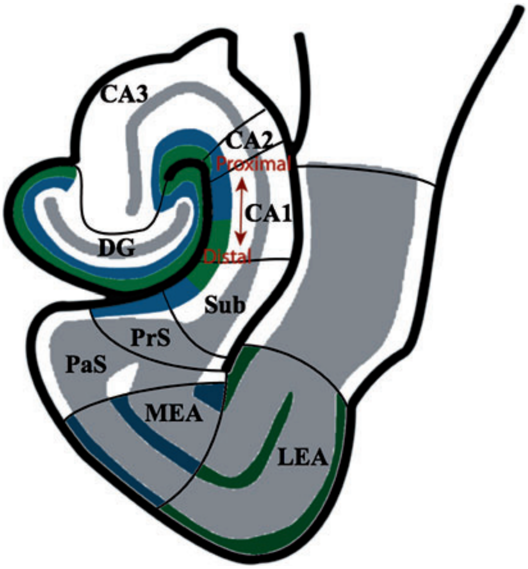

Hippocampus, Fig. 1 The hippocampal formation including the cornu ammonis subregion (*CA1*, *CA2*, *CA3*), dentate gyrus (*DG*), subiculum (*Sub*), presubiculum (*PrS*), parasubiculum (*PaS*), and lateral (*LEA*) and medial (*MEA*) entorhinal area (Permission granted by Lara Rangel and Jon Rueckemann)

(affectionately known as Darwin's Bulldog) grew irritated and systematically dissected multiple monkeys to collect evidence against Owen's case. Huxley and Owen's debate became public in 1860 at a debate on evolution at Oxford University, culminating in a heated series of lectures and publications between Owen and Huxley, eventually leading to Owen's more systematic refutation by William Henry Flower in 1862. The "Great Hippopotamus Test" was immortalized in Victorian culture in 1862 by Charles Kingsley who published a children's book *The Water-Babies, A Fairy Tale for a Land Baby* satirizing the incident. By 1866, Owen had retracted his previous statements about monkeys lacking this structure and admitted his mistaken view in his book *On The Anatomy of Vertebrates* (Gross 1993).

In 1873, Golgi developed a new method of using silver staining techniques to uncover the structure of the axons, cell bodies, and dendrites of neurons. Ramon y Cajal (1911) perfected Golgi's method and used this method to study the connectivity of individual neurons in hippocampus. In 1934, Cajal's student Lorente de No provided the anatomical descriptions of the CA regions that are widely accepted today (Falougy and Benuska 2006). In 1937, Papez proposed that emotional experience was rooted in connectivity between the hypothalamus and medial temporal areas. Building on Papez's theory, (MacLean 1949) suggested that the hippocampus along with the amygdala, septum, and hypothalamus was part of the "visceral brain" or "limbic system" which was primarily recruited for the generation of emotional experiences.

In the 1950s, the Montreal Neurology Group lead by Wilder Penfield searched for the mechanistic origins of temporal lobe epilepsy (Penfield et al. 1952). A significant advance in identifying the functional role of hippocampus came from the famous case study of patient H. M. (after his death identified as Henry Molaison). H. M. suffered from major temporal lobe seizures and lapses of consciousness multiple times daily, and Dr. William Beecher Scolville decided to remove the hippocampus bilaterally with hopes of relieving the symptoms. After the removal of his hippocampus (along with surrounding tissue) bilaterally, H. M. was unable to form new episodic memories, having a condition known as anterograde amnesia. Brenda Milner gave H. M. a battery of psychological tests to empirically determine the memory deficits of bilateral hippocampal lesions in humans and demonstrated that other lesions to related medial temporal areas like the amygdala did not have the same types of memory deficits (Scoville and Milner 1957).

While the hippocampus was established as playing an important role in emotion and memory formation, by the early 1970s, the discovery of spatially selective cells, known as "place cells" in the rodent hippocampus, led the field to focus primarily on its role in navigation (O'Keefe and Dostrovsky 1971). This fascinating one to one mapping between cellular function and the external environment was conducive to extensive empirical investigation. Consideration of the hippocampus' role in temporal processing and context have served a unifying role between the navigation literature on hippocampal function in rodents to that of the formation of episodic memory.

Hippocampal Neuroanatomy: Gross Anatomy and Microcircuitry

The hippocampus is a three layered brain structure described as being made up of the cornu ammonis (CA1, CA2, CA3) and dentate gyrus. The first layer is known as the stratum oriens, which has a mixture of afferent and efferent projections and interneurons. The second layer is called the stratum pyramidale. The third layer is known as the stratum moleculare, which in CA3 is further divided into the stratum lucidum, stratum radiatum, and the stratum lacunosum-moleculare. The CA regions and DG regions are present throughout the dorsal, intermediary, and ventral portions of hippocampus (Amaral and Witter 1989; van Strien et al. 2009).

The trisynaptic loop is the canonical circuit described by Ramon y Cajal and De No (1911) which reciprocally connects cortex and hippocampus completing what is known as the cortico-hippocampal loop (Andersen 1975). The first synapse of the trisynaptic circuit is made by pyramidal cells in lateral entorhinal cortex (lEC) layer II, whose axons perforate through the subiculum, synapsing onto the granule cells of the dentate gyrus. These bundles are known as the perforant pathway (Amaral and Witter 1989). The mossy fiber pathway is a set of axons which project from the granule cells of the dentate gyrus to the pyramidal cells of CA3 forming the second synapse of the trisynaptic circuit (Van Strien et al. 2009). Pyramidal cells from CA3 project axons, known as the Schaffer collaterals, up to CA1 where they converge on CA1 pyramidal cells' apical dendrites. This is where CA1 pyramidal cells project back to deep layers of the entorhinal cortex, completing the hippocampal-cortical loop (Amaral and Witter 1989; Van Strien et al. 2009). The trisynaptic pathway is a robust pathway present in all mammals and is a general organizing principle for understanding hippocampal processing.

The trisynaptic circuit describes a robust set of connections, but there is additional connectivity which was not included in the canonical circuit. There are also projections from medial and lateral entorhinal cortex onto CA1, with lateral entorhinal inputs converging onto the dendrites of CA1 cells located closer to subiculum, and the medial entorhinal inputs converging onto the cells closer to CA3 (Steward 1976). Interestingly, area CA2 has been historically left out of the circuit altogether. CA2 pyramidal cells project onto CA1 dendrites, and have been shown to drive CA1 activity when stimulated. It has been found that the granule cells in the dentate gyrus also converge onto CA1 cells and also project axons to area CA2. CA2 pyramidal cells receive input from the supramamillary nucleus and vassopressinergic cells from the paraventricular nucleus of the hypothalamus (Dudek et al. 2016).

In regards to extrahippocampal connections, the parahippocampal region is a six layered cortical region highly integrated with the hippocampal formation and includes the presubiculum, parasubiculum, entorhinal cortex (medial and lateral), perirhinal cortex, and postrhinal cortex. The hippocampus has major output pathways to the subiculum, retrosplenial cortex, parietal cortex, and lateral septal nucleus. The hippocampus also has connectivity with the medial prefrontal cortex, which supports temporal sequence processing (Van Strein et al. 2009).

Computational Roles of Hippocampal Subregions

The dentate gyrus has many more neurons than the inputs it receives from entorhinal cortex, which then project back down to a smaller number of neurons in CA3. This structural property suggests that the dentate gyrus may have an ability to perform a computational process known as pattern separation. This separation process involves taking highly similar inputs, projecting those input patterns onto a larger population of cells, allowing for the generation of more differentiated output pathways than the initial inputs (Deng et al. 2010). The perforant pathway between the EC and the DG was the site of the discovery of long-term potentiation (LTP) (Bliss and Lomo 1973). Long-term potentiation is believed to be a primary mechanism that governs neural plasticity, which suggests that synapses between neurons become strengthened when neurons have action potentials close together in time. The dentate gyrus is the only site of neurogenesis in the hippocampus, allowing for new cells to be born throughout an organism's life (Gage 2002). Theories and computational models of dentate gyrus suggest that these newborn neurons allow for the temporal separation of similar events that take place in similar contexts (Rangel et al. 2014).

CA3 has two types of reciprocal connectivity to allow its theorized function of pattern completion. CA3 excitatory pyramidal cells project heavily onto themselves forming what is known as the "longitudinal association pathway." These excitatory connections are believed to allow for heteroassociation, which is the ability to recall a complete representation or sequence only given a partial subset of the original (McNaughton and Morris 1987). CA3 pyramidal cells also project onto inhibitory basket cells which allow for recurrent inhibition.

Place Cells and the Cognitive Map

O'Keefe and Dostrovsky discovered "place cells" in the hippocampus and published the results in 1971. They reported that about 10% of the cells they recorded from in the CA1 region responded to an animal's spatial position while facing a certain direction. This led O'Keefe and Nadel (1978) to develop a spatial theory of hippocampus building on the work of Tolman, suggesting that these neurons represented an allocentric "cognitive map" of the environment. Tolman developed a cognitivist account of purposive and goal-oriented behavior and suggested that motion through an environment could be represented topologically allowing for the identification of "cognitive" maps. CA1 place cells have receptive field known as place fields, which correspond to an increased firing rate while the animal is in a certain position in the environment (O'Keefe and Nadel 1978). Neurons in the dorsal region respond more robustly to spatial relationships, while the ventral regions coded more for emotional and social stimuli. Head-direction cells, which respond to different positions of the head relative to the body of the animal, have been discovered in the septal presubiculum, entorhinal cortex, retrosplenial cortex, thalamus and mammillary nucleus (van Strien et al. 2009). McNaughton and colleagues suggest that the hippocampus is part of a system for path integration. This system involves the integration of place cells with head-direction cells in the presubiculum, cortex, and thalamus (McNaughton et al. 1996). The cognitive map also involves other more complex abstract spatial representations supported by circuits between hippocampus, parietal cortex, and retrosplenial cortex (Alexander and Nitz 2015).

The Morris water maze is a popular experimental paradigm used to test hippocampal dependent memory. In this task, a rat is placed in a large circular pool of milky or opaque water where there is a hidden platform that allows the rat to escape from the water. The rat initially explores the environment randomly until finding the platform, and after the rat climbs on top of the platform the rat is removed from the maze. When placed back in the water maze, given that there are no local cues indicating the location of the platform, the animal depends on its memory of the platform's location relative to the global environment (Morris 1984). It has been shown that animals with hippocampal lesions have significantly impaired performance on this spatial memory task.

Hippocampal Rhythms: Theta and Sharp Wave Ripples

In rats and other animals, including rabbits, cats, and monkeys, the local field potential in the hippocampus is dominated by the hippocampal theta rhythm, which is an oscillation that occurs at approximately 5–10 Hz. The local field potential is an electrical potential that is measured by embedding wires in the extracellular matrix of a group of neurons (Buszaki et al. 2012). The theta oscillation increases in amplitude when the animal is moving throughout the environment and reduces when the animal is still. Hippocampal theta has been determined to be a dynamic wave that travels along the septotemporal axis of the hippocampal region (Lubenov and Siapas 2009). The origins of the theta oscillation are still unclear, but there is evidence to suggest that cholinergic cells in the medial septum might act as "pacemakers" for the hippocampal theta rhythm. The supramammillary nucleus of the thalamus with heavy connectivity to the septum is also a candidate for acting as a theta pacemaker (Buzsaki 2006). It is also possible that hippocampal interneurons play a role in regulating theta, as they are the only cell types that receive projections from medial septum, and also project from hippocampus to medial septum (Freund and Antal 1988).

CA1 place cells have been demonstrated to organize their action potentials to particular phases of the theta oscillation according to their temporal relationships. Phase precession is the phenomena where place cells coordinate their action potentials to different phases of the hippocampal theta oscillation representing where the animal currently is, where it is going, and where it has been (Buzsaki 2006). Models of hippocampal memory function suggest that this phase-dependent coding scheme might be a method for organizing memory encoding and retrieval (Hasselmo and Stern 2014).

Another rhythmic pattern in the hippocampal local field potential is the sharp wave ripple, which is a 140–200 Hz transient burst that occurs during wake and sleep (Buzsaki 2006). Hippocampal ripples have been observed in mice, rats, rabbits, monkeys, and humans (Logothetis et al. 2012). In awake animals, after running through a sequence of places tracked by place cell activity, when they stop running, sharp wave ripples occur. During those stop times, place cells fire in coordinated phase with the oscillatory ripples, in fact it was found that it was the same sequence of place cells rapidly firing in reverse temporal order (Foster and Wilson 2006). It is believed that this sequential replay is a functional process which allows for memory consolidation.

Temporal Coding

The hippocampus not only has a part in computing the animal's position in space but also information related to time. Lesions of the hippocampus can result in deficits in the recall of temporal order. In one task testing temporal order recognition, rats were trained to run through random sequences on an 8-arm radial maze. In the test phase, rats were presented with two arms simultaneously and were tasked with running through the arm which appeared earlier in the training sequence. Rats with lesions of the hippocampus performed poorly as compared to control rats on arms that were in close temporal proximity to each other (Chiba et al. 1994). CA1 place cells have also been observed to selectively fire to odors presented in a sequence. Similarly to the radial maze, the two temporally related odors were presented simultaneously and the rat was given a reward if it chose the odor that was presented earlier in the training sequence. This suggests that there are additional temporal dimensions that are coded along with the spatial mapping functions of CA1 place cells (Eichenbaum 2014).

Conclusion

The hippocampus is a complex brain structure that carries out functions that are central to an organism's sense of spatial relations and memory formation. Future studies will be tasked with integrating the functional processes related to spatial maps and episodic events. Multiple studies have also been conducted where rats navigate a virtual reality environment, and it has been found that place cell activity is diminished to a significant degree (Aghajan et al. 2015). Additionally, CA1 place cells have recently been shown to map onto more than just allocentric space. A recent study showed then when a rat was given a joystick to control an auditory signal, that CA1 place cells mapped onto auditory dimensions suggesting that it might be necessary to broaden the definition of "place" with regard to "place cell" activity (Aronov et al. 2017). There are many questions to be answered about the relation between hippocampal function and structure, and will likely be the central focus of analyses for years to come with hopes to understand the representation of events, space, and time in the brain.

Cross-References

- ▶ Action Potentials
- ▶ Axon
- ▶ Entorhinal Cortex
- ▶ Hypothalamus
- ▶ Medial Entorhinal Area
- ▶ Neuron

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