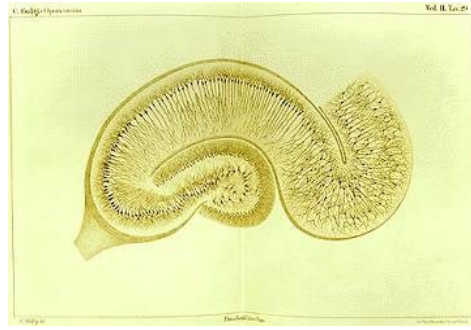
Lesson (19)

A cellular view of the hippocampus

HIPPOCAMPUS means sea horse

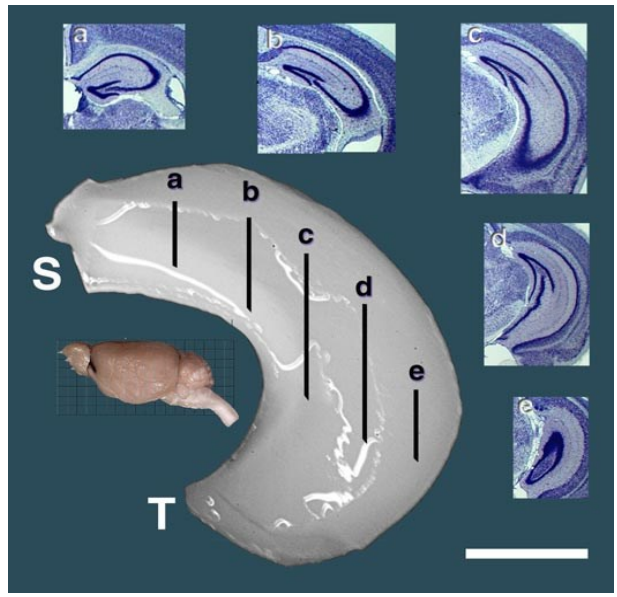


By C.Golgi

(*hippo* = horse, *kampos* = sea monster, Greek)

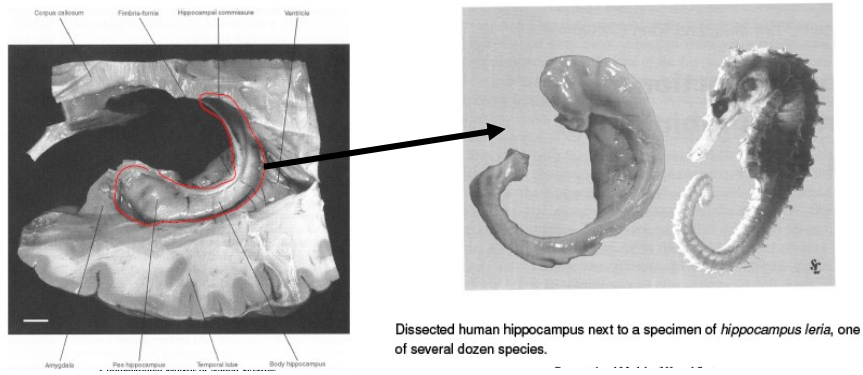
cylindrical structure whose longitudinal axis forms a semicircle around the thalamus
among the best characterized cortical structures

The rat hippocampus



The hippocampus in the human brain

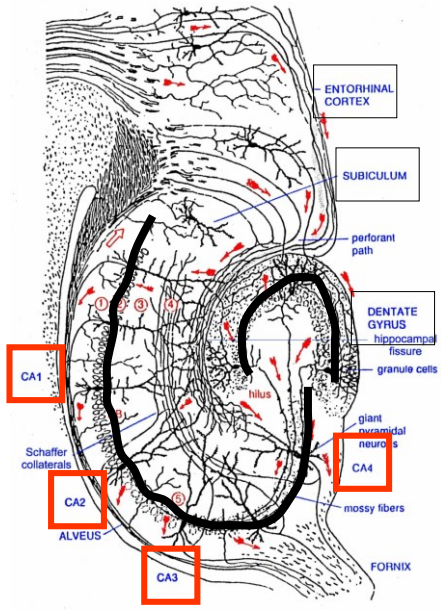
The hippocampus in the human brain



Dissected human hippocampus next to a specimen of *hippocampus leria*, one of several dozen species.

The human hippocampus has a 1000 times larger volume than the rat hippocampus

Anatomical subdivisions of the hippocampus

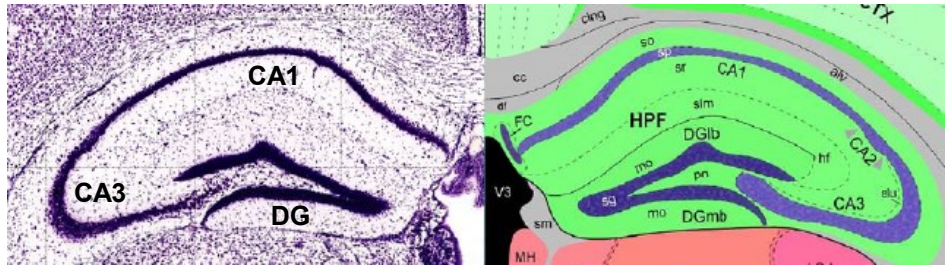


Hippocampus proper can be divided into four regions:

CA1, CA2, CA3 and CA4 from the Latin *Cornu Ammon*, or Ammon's horn, because of its resemblance to a ram's horn that was bear by the ancient Egyptian God **Ammon**.

Another nomenclature refers to the **hippocampal formation** (or **hippocampal region**) including also the dentate gyrus (DG), the subiculum and the entorhinal cortex.

New anatomical data: the Allen Reference Atlas

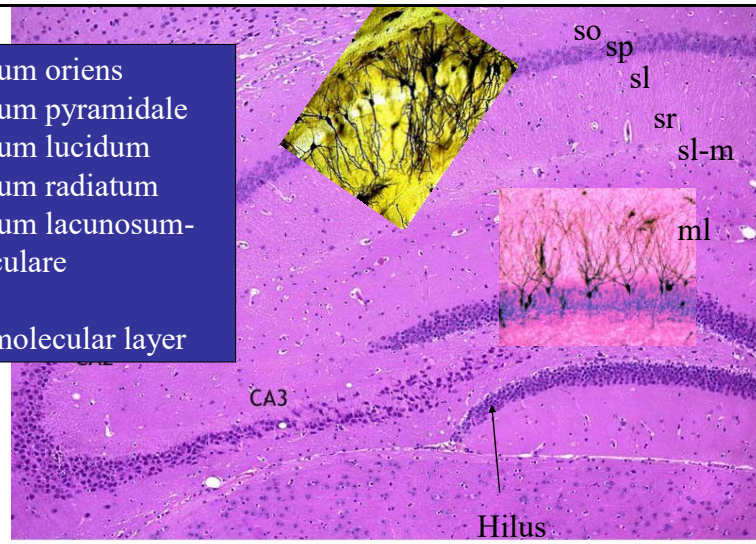


Allen Reference Atlas (Allen Institute for Brain Science - Seattle, USA)

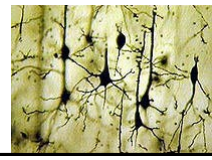
http://mouse.brain-map.org/

- Stratum oriens
- Stratum pyramidale
- Stratum lucidum
- Stratum radiatum
- Stratum lacunosum-moleculare

- ml=molecular layer

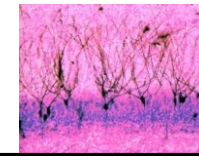


www.deltagen.com/.../nervous/ cerebrum_hippo_10x.htm



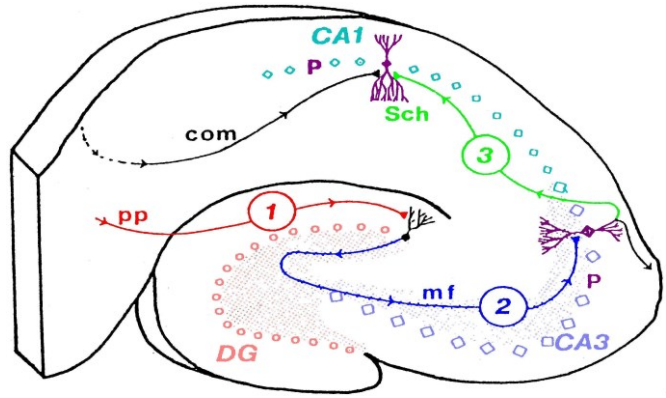
CA1-CA3: pyramidal neurons

Dentate Gyrus: granule cells



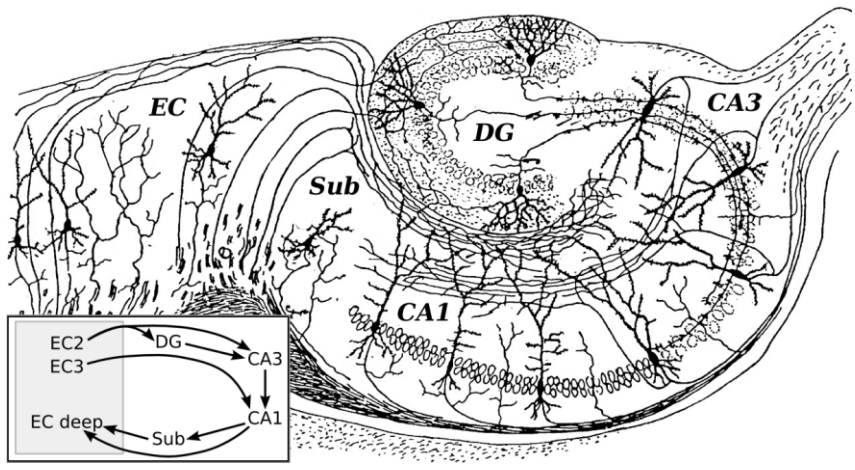
The tri-synaptic circuit in the rat hippocampus

PP=Perforant path
mf=mossy fibers
SCh=collateral Schaffer fibers



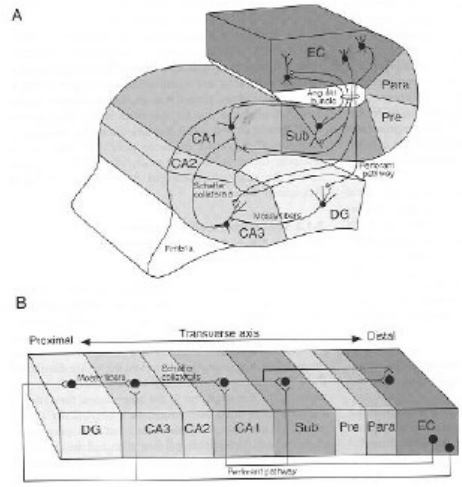
The tri-synaptic circuit of the hippocampus

(shown using a modified drawing by Ramon y Cajal)

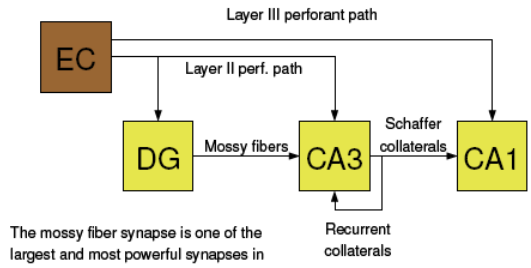


DG: dentate gyrus. Sub: subiculum. EC: entorhinal cortex

Connectivity Is Mostly Uni-Directional

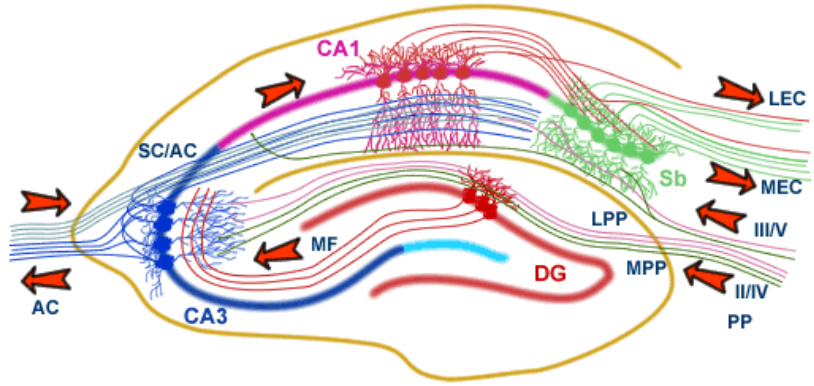


Basic Circuit



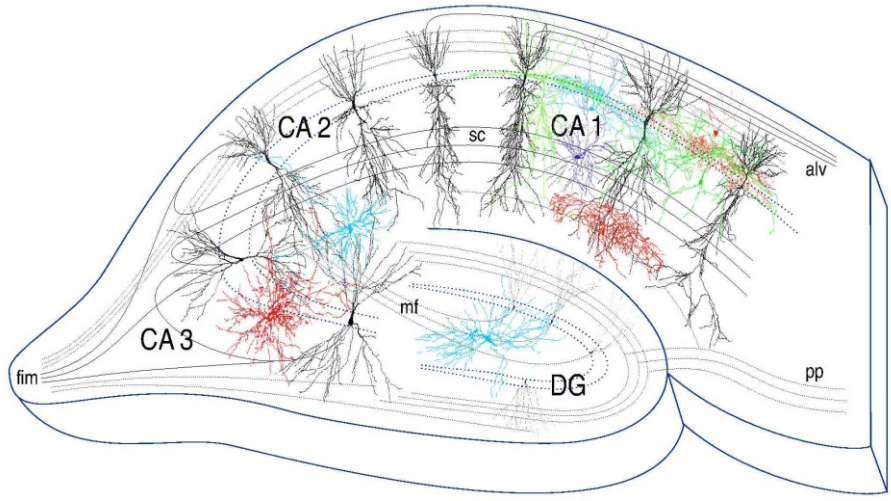
The mossy fiber synapse is one of the largest and most powerful synapses in the brain.

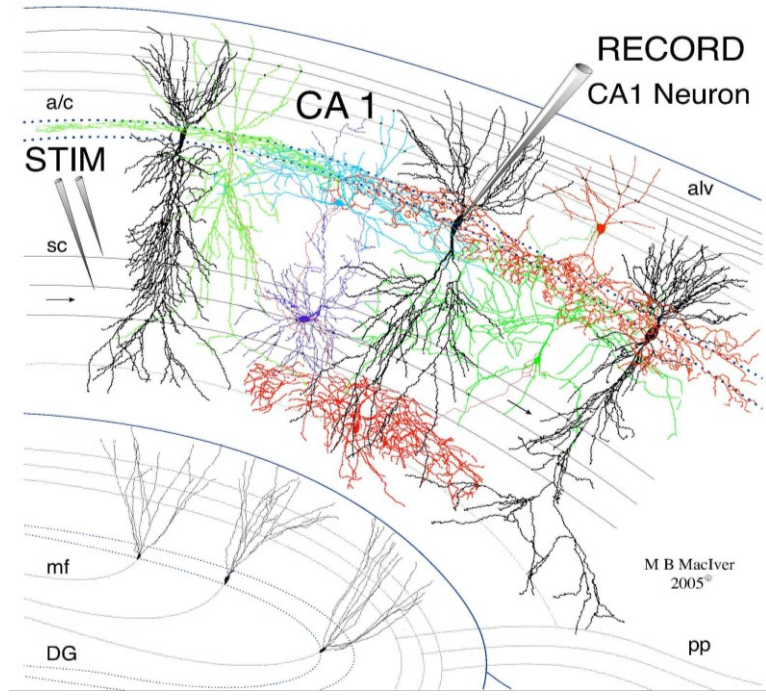
The hippocampal circuit



The Hippocampal Network: The hippocampus forms a principally uni-directional network, with input from the Entorhinal Cortex (EC) that forms connections with the Dentate Gyrus (DG) and CA3 pyramidal neurons via the Perforant Path (PP - split into lateral and medial). CA3 neurons also receive input from the DG via the mossy fibres (MF). They send axons to CA1 pyramidal cells via the Schaffer Collateral Pathway (SC), as well as to CA1 cells in the contralateral hippocampus via the Associational Commissural pathway (AC). CA1 neurons also receive input directly from the Perforant Path and send axons to the Subiculum (Sb). These neuron in turn send the main hippocampal output back to the EC, forming a loop.

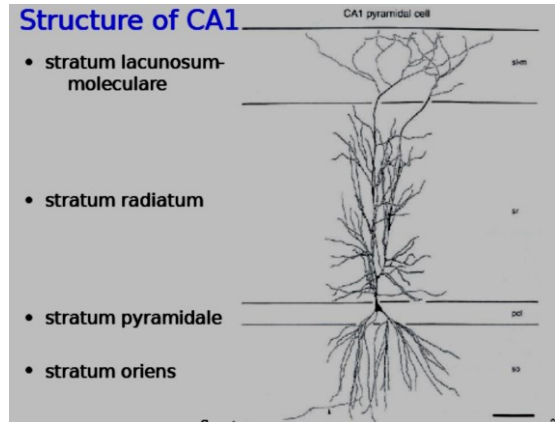
Cellular organization of the hippocampus proper





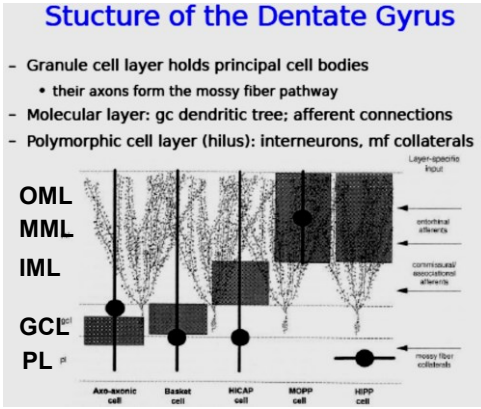
Structure of CA1

- stratum lacunosum-moleculare
- stratum radiatum
- stratum pyramidale
- stratum oriens

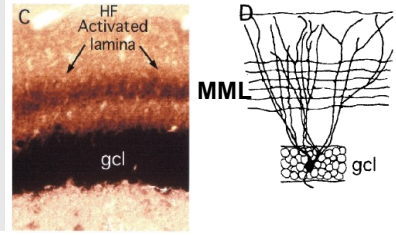


From Computational Models of Neural Systems - David S. Touretzky

Both the hippocampus and the DG are three-layered cortices



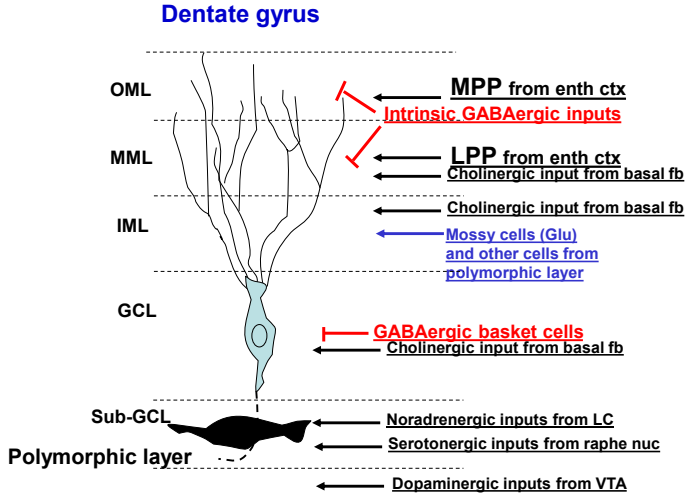
The three fundamental layers of the DG are:
The polymorphic layer or hilus
The granular layer or *stratum granulosum*
The molecular layer or *stratum molecolare*



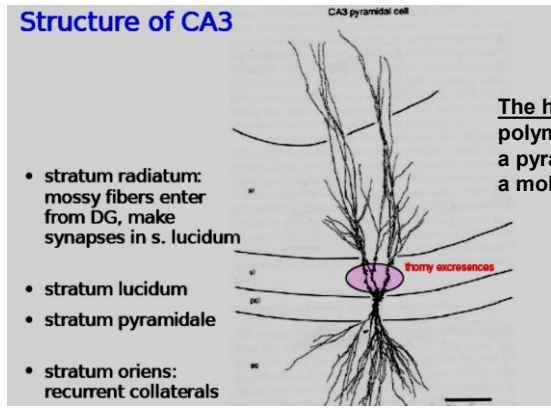
From Steward & Worley PNAS 2001

From Computational Models of Neural Systems - David S. Touretzky

Different layers have different connections

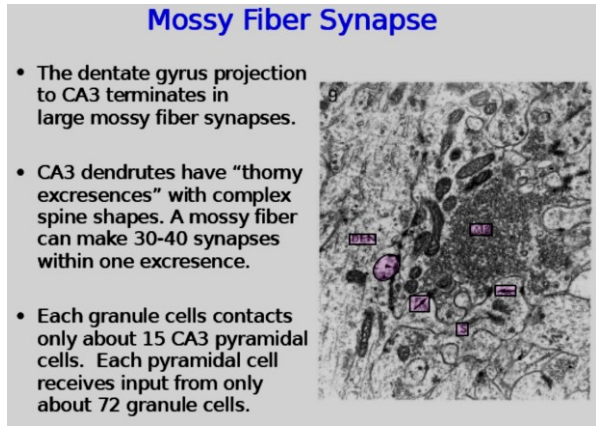


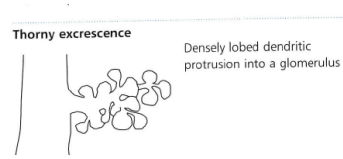
Both the hippocampus and the DG are three-layered cortices



<u>The hippocampus proper consists of a:</u>
polymorphic layer or *stratum oriens*
a pyramidal layer or *stratum piramidale*
a molecular layer or *stratum radiatum.*

From Computational Models of Neural Systems - David S. Touretzky





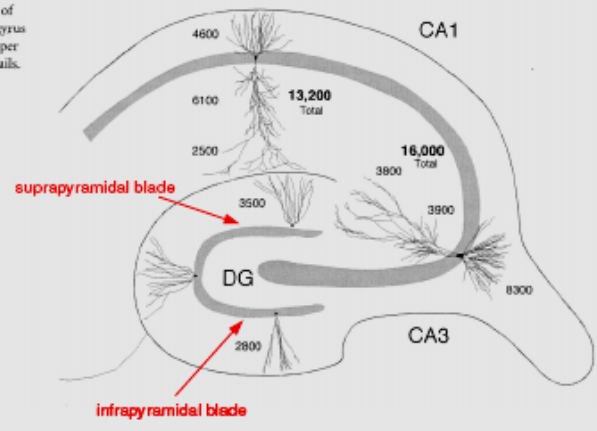
From Computational Models of Neural Systems - David S. Touretzky

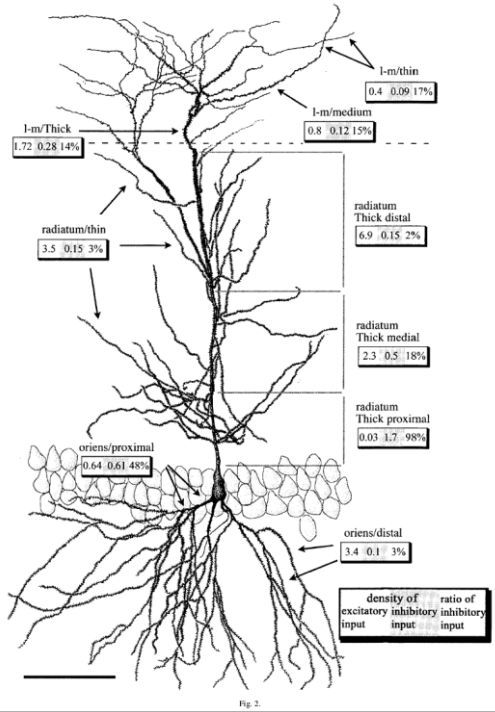
Some Numbers for the Rat

- Dentate Gyrus
  - 1.2 million granule cells
  - 4K basket cells
  - 32K hilar interneurons (20K mossy cells)
- CA3/CA1
  - 330K /420K pyramidal cells
  - various interneurons
- Entorhinal cortex layer II
  - Around 200K cells (20% interneurons?)
- Subiculum
  - Around 180K cels

Dendritic Arborization of Principal Cells

Figure 3–15. Dendritic arborization of the principal cells in the rat dentate gyrus (granule cells) and hippocampus proper (pyramidal cells). See the text for details.

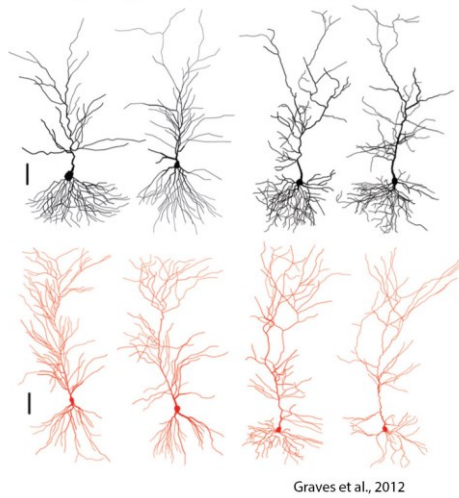




The integrative properties of neurons depend strongly on the number, proportions and distribution of excitatory and inhibitory synaptic inputs they receive.

Neuroscience. 2001;102(3):527-40.
Megias M, Emri Z, Freund TF, Gulyas AI.

Two types of pyramidal neurons in CA1 and subiculum

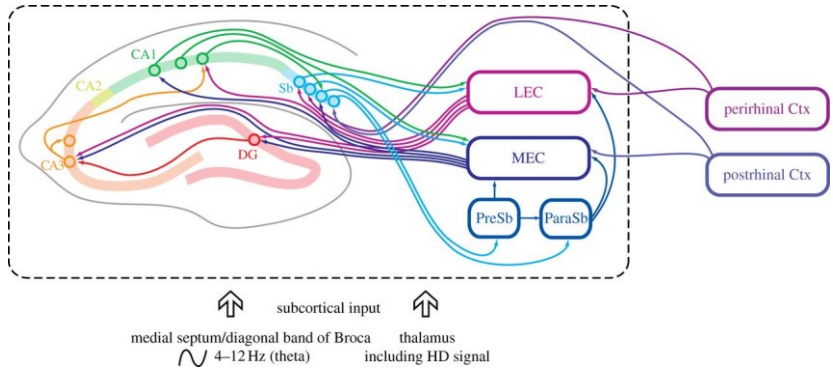


Graves et al., 2012

Spatial and non-spatial information remain largely segregated in parallel processing streams through anatomically separate regions of CA1. These CA1 pyramidal cells in turn project to separate areas of the subiculum that contain predominantly either late-bursting or early-bursting cells, which subsequently transmit hippocampal output to divergent brain regions

Space in the brain: how the hippocampal formation supports spatial cognition

MEC is more involved in map-like spatial processing than the LEC
But one function of the LEC is to code for the remembered locations of objects



Classic trisynaptic pathway consists of projection from entorhinal cortex (LEC: lateral entorhinal cortex; MEC: medial entorhinal cortex) to dentate gyrus (DG), from DG to CA3, and from CA3 to CA1. Entorhinal input also consists of direct monosynaptic LEC and MEC projections to CA3, to CA1, and to subiculum (Sb).

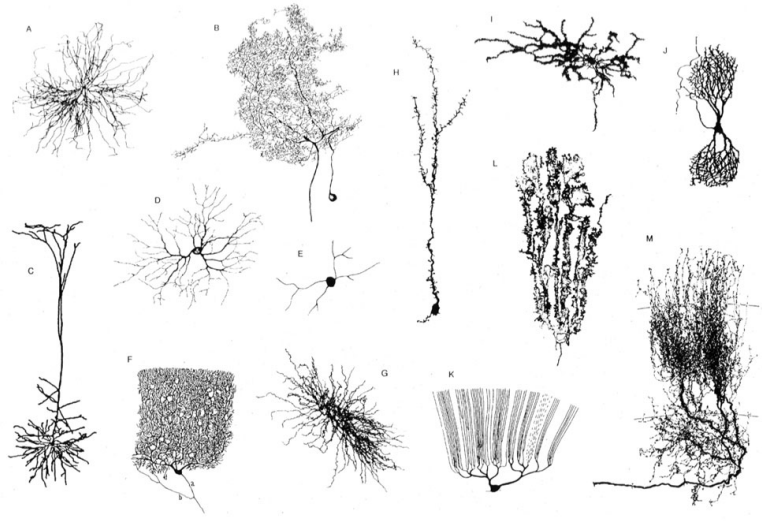
Connectivity of CA1 neurons

- A single pyramidal cell has approximately 12,000 micron dendrites and receives around 30,000 excitatory and 1700 inhibitory inputs, of which 40 % are concentrated in the perisomatic region and 20 % on dendrites in the stratum lacunosum-moleculare.
- Proximal apical and basal strata radiatum and oriens dendrites are spine-free or sparsely spiny. Distal strata radiatum and oriens dendrites (forming 68.5 % of the pyramidal cells' dendritic tree) are densely spiny; their excitatory inputs terminate exclusively on dendritic spines, while inhibitory inputs target only dendritic shafts.
- The proportion of inhibitory inputs on distal spiny strata radiatum and oriens dendrites is low (approximately 3 %). In contrast, proximal dendritic segments receive mostly (70-100 %) inhibitory inputs. Only inhibitory inputs innervate the somata (77-103 per cell) and axon initial segments.
- Dendrites in the stratum lacunosum-moleculare possess moderate to small amounts of spines. Excitatory synapses on stratum lacunosum-moleculare dendrites are larger than the synapses in other layers, are frequently perforated (approximately 40 %) and can be located on dendritic shafts. Inhibitory inputs, whose percentage is relatively high (approximately 14-17 %), also terminate on dendritic spines.

Rat Connectivity

- Perforant path projection to DG
  - Around 4500 spines per granule cell (75% from EC)
  - One EC cells makes about 18,000 synapses with granule cells
- CA3: three distinct inputs
  - 50-80 mossy fibers from DG
  - 3,500 perforant path synapses from EC II
  - 12,000 recurrent collaterals from other CA3 cells
    - 8,000 to basilarl dendrites (stratum oriens)
    - 4,000 to apical dendrites (stratum radiatum)
- CA1: inputs from CA3 and EC
  - From CA3 Schaffer collaterals: 4,500 basilar, 6500 apical synapses
  - From EC layer III: 2,500 synapses

Cellular diversity in the hippocampus



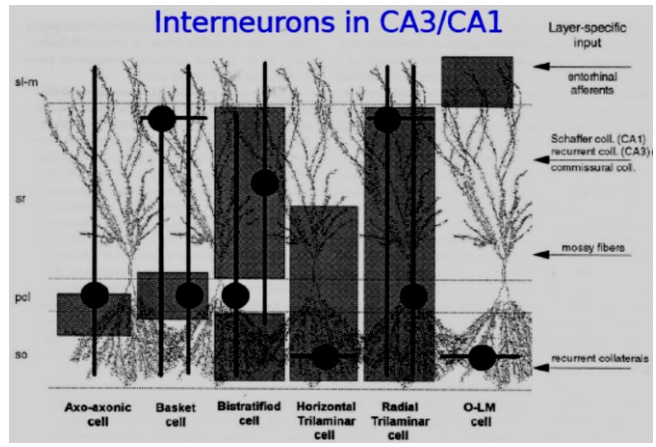
Cellular diversity in the hippocampus = different connectivity

Stratum lacunoso molecularis

stratum radiatum

stratum piramidale

stratum oriens



From Computational Models of Neural Systems - David S. Touretzky

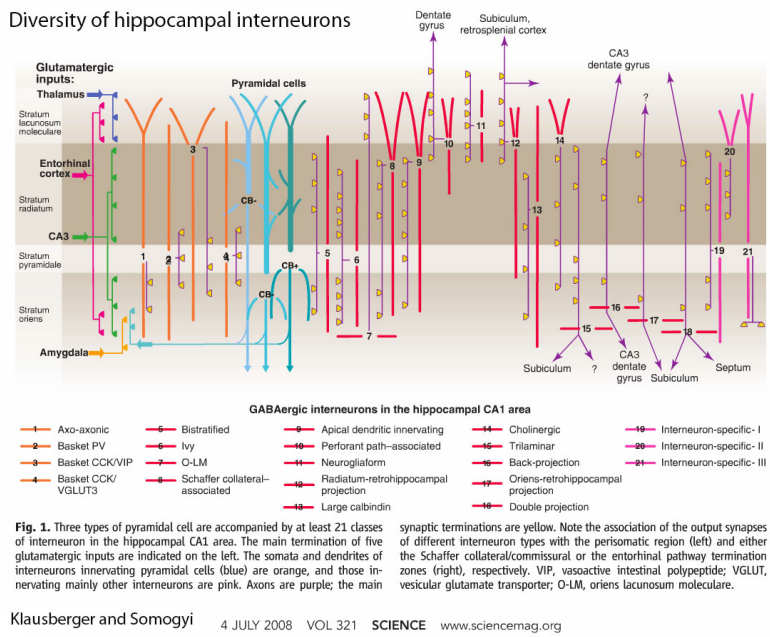


Fig. 1. Three types of pyramidal cell are accompanied by at least 21 classes of interneuron in the hippocampal CA1 area. The main termination of five glutamatergic inputs are indicated on the left. The somata and dendrites of interneurons innervating pyramidal cells (blue) are orange, and those innervating mainly other interneurons are pink. Axons are purple; the main synaptic terminations are yellow. Note the association of the output synapses of different interneuron types with the perisomatic region (left) and either the Schaffer collateral/commissural or the entorhinal pathway termination zones (right), respectively. VIP, vasoactive intestinal polypeptide; VGLUT, vesicular glutamate transporter; O-LM, oriens lacunosum moleculare.

Klausberger and Somogyi 4 JULY 2008 VOL 321 **SCIENCE** www.sciencemag.org

What Does the Hippocampus Do?

- Formation of new episodic memories?
  - Anterograde amnesia (H.M. and others)
- Cognitive map?
  - Place cells in rats; spatial attention cells in monkeys
- Configural association theory?
  - Lesioned rats are impaired on tasks requiring them to recognize cue configurations

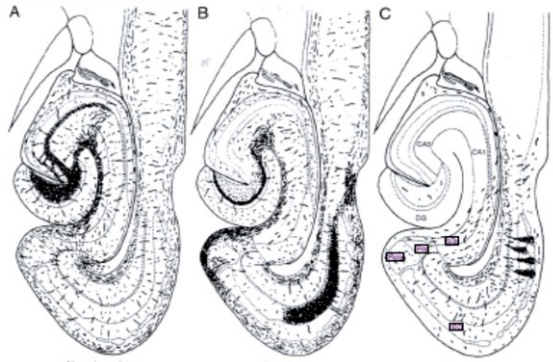
The Hippocampus Is Very Well Connected to Other Brain Areas

Connected via EC and fimbria-fornix pathway to:

- Prefrontal / orbitorfrontal cortices
- Cingulate cortex
- Piriform cortex
- Perirhinal and Postrhinal cortices (sensory)
- Striatum
- Amygdala
- Septum
- Mammillary bodies
- Thalamus
- Hypothalamus

Neuromodulatory Projections to HC

Figure 3–21. Line drawing of horizontal sections through the rat hippocampal formation shows the distribution of *A.* noradrenergic, *B.* serotonergic, and *C.* dopaminergic fibers. (*Source:* Adapted from Swanson et al., 1987.



Noradrenaline
locus coeruleus

Serotonin
raphe nuclei

Dopamine
substantia nigra

NA: Attention
5HT: Mood
DA: Reward
ACh: Novelty

acetylcholine
medial septum