TNS Journal Club: Interneurons of the Hippocampus, Freund and Buzsaki

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Introduction

- *Interneuron* $\stackrel{\text{def}}{=}$ GABAergic non-principal cell
- Usually involved in *local circuitry*.
- Unifying review of morphological, neurochemical and physiological features of interneurons in the hippocampus.
- Massively complex:
  - Loads of facts ($\sim 10^4$) which are often exceptions to previous facts.
  - (Many) Life-times of work (original studies are 100 years old).
  - Dictionary like description is an exponential task.
- Quite an old paper (9yrs) and experimental focus is on rodents.

Why make a career out of interneurons?

- Only 10% of cells are interneurons - so why bother?

But:

- Primary cells are covered with synapses from interneurons (interneuron $\rightarrow$ 1000-3000 pyramidal cells)

The authors of this paper believe:

- Interneurons have a crucial role in regulating the complex interactions between principal cells.
- Interneurons represent a key to the understanding of network operations.
- In contrast to primary cells in a hippocampal subfield, the afferent and efferent connectivity of interneurons show *great variation* thereby enabling them to carry out multiple tasks.

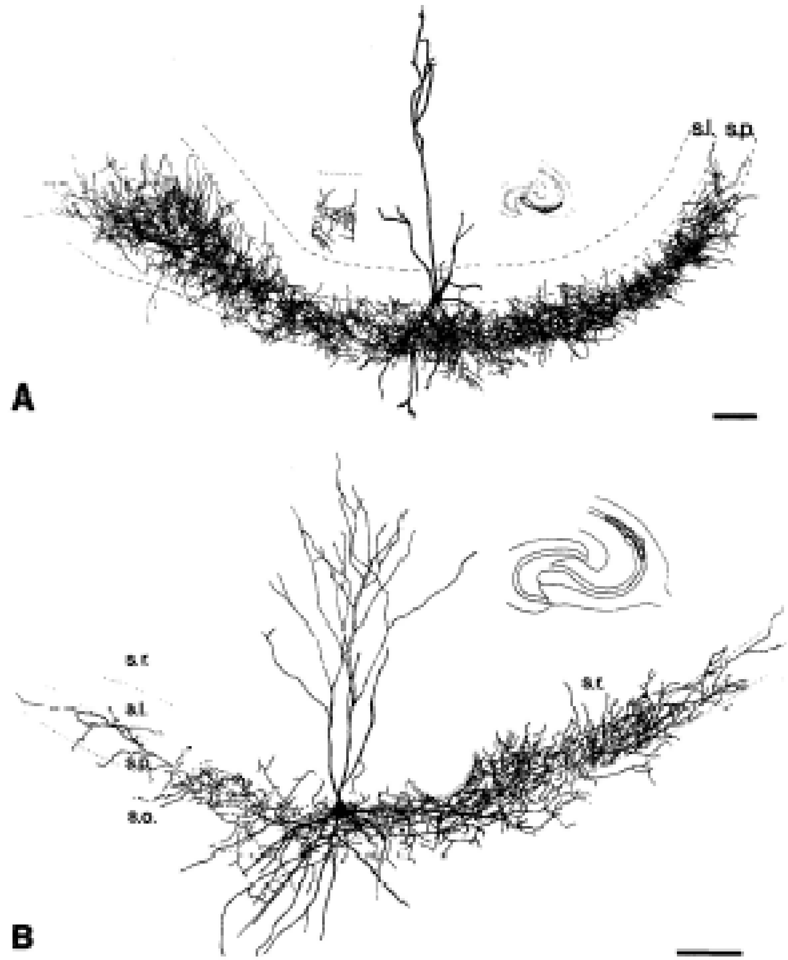
Morphology

- Look at data from a wide range of *single cell labelling* studies
- *Classification* of interneurons based on *dendritic and axonal arborization* (branching) patterns, the location of the *cell body* and the *afferent* and *efferent* connection types.

Two examples - connections

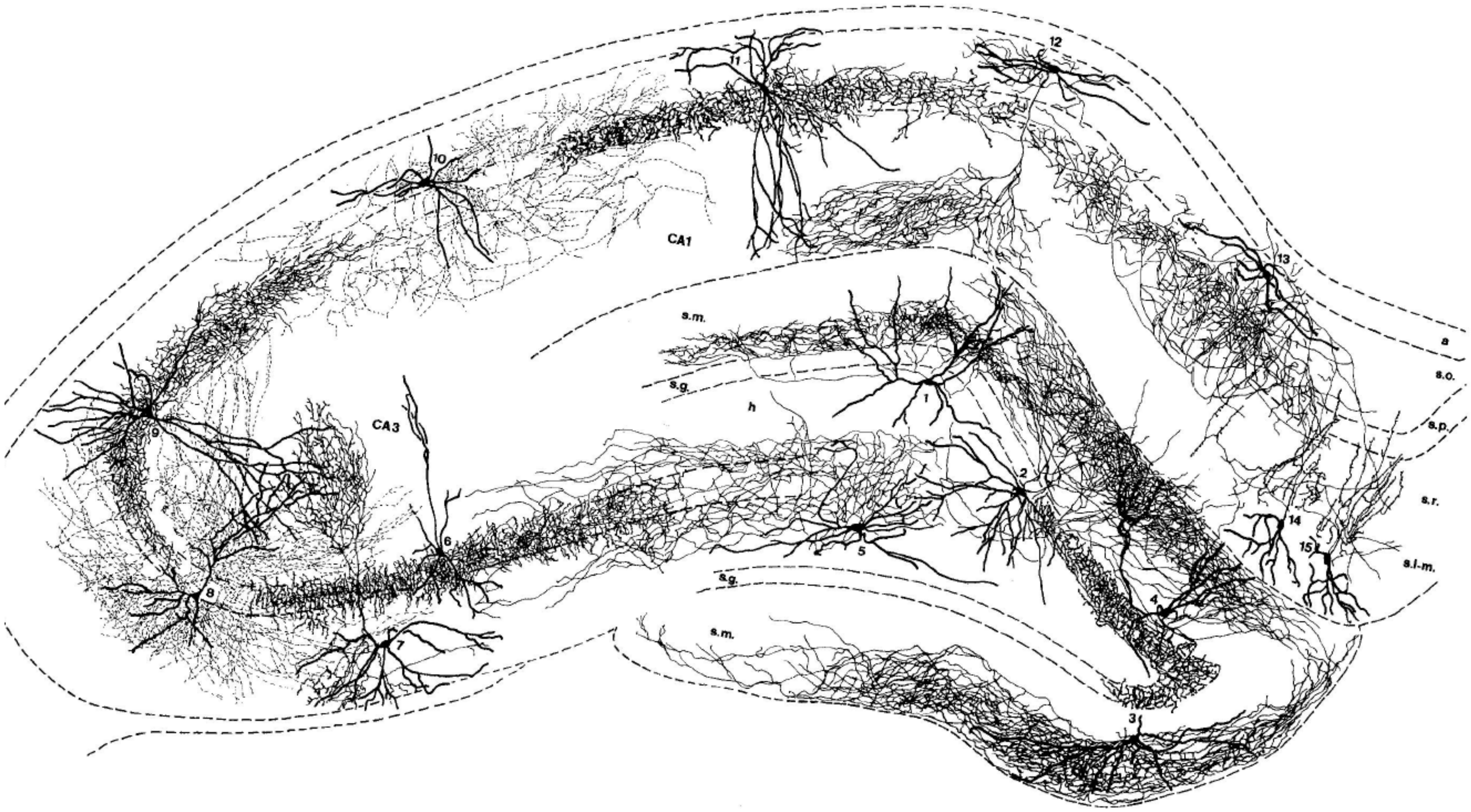
- Chandelier or Axo-axonic cells
  - Characteristic axon termination forming rows of boutons aligned parallel with the initial segments of principals.
  - Highly specific termination: Exclusive post synaptic elements are axon initial segments of pyramidal cells.
- Basket Cell: at least 5 different types
  - heterogeneous afferent connections
  - innervate cell bodies of principal cells

Two examples-morphology



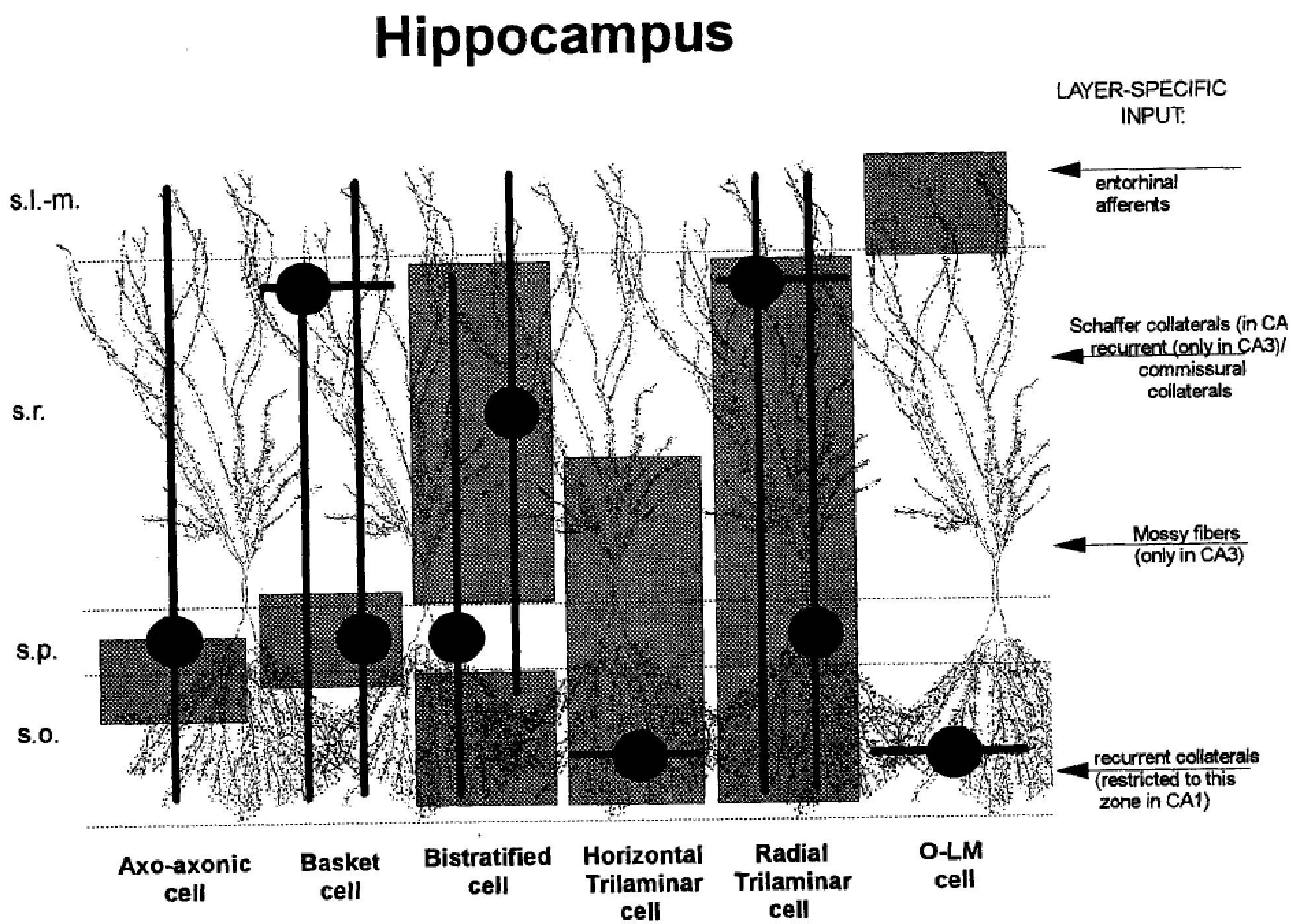
Axo-axonal (top) and Basket cells (bottom).Quite similar: Dendritic trees tufted and span all layers. Small number of basket cell collaterals penetrate the statum radiatum. Numerous vertically oriented axon terminal segments in the axo-axonal cells.

Morphological classification



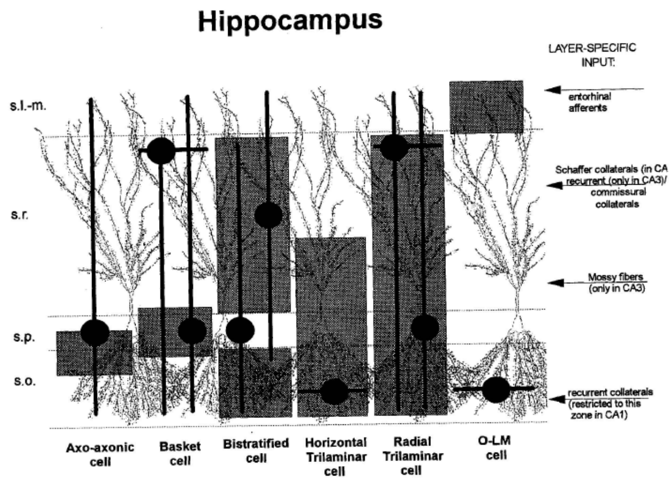
Superposed pictures of real neurons in situ 6. Axo-axonic, 11.Basket cell of CA1, 7. O-LM cell of CA3 - feedback interneuron

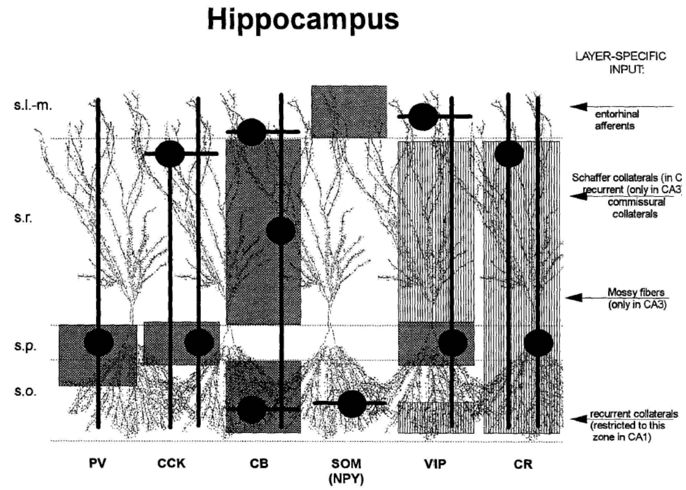
Morphological classification

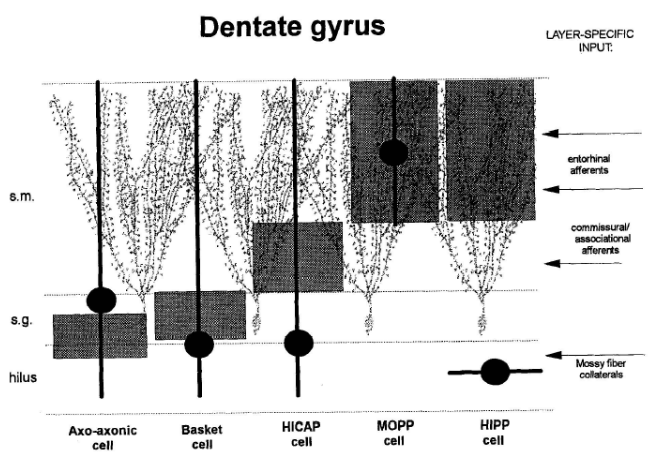


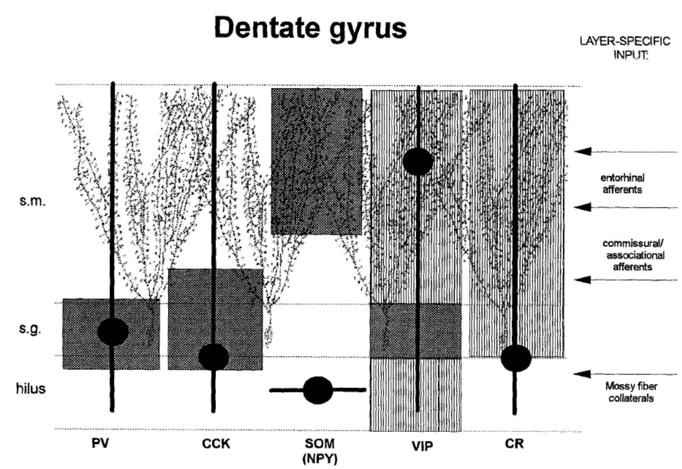
Summary of morphological classification: nb arborized axons correspond closely to field's afferents

Neurochemical classification









Produced using a sequence of stains, final for neuropeptide in synaptic bouton.

Subcortical innervation of hippocampal interneurons

- Generally comes from relatively small groups of neurons and activate GABAergic interneurons which in turn exert GABAergic inhibition onto large populations of principal cells.

- Two pathways from the septum:
  - GABAergic pathway into the CA3 subfield
  - *Cholinergic* pathway direct to principal cells in DG,CA1 and CA3

- *Serotonergic* Raph-Hippocampal Projection (from median raphe nucleus)
  - two types of afferents possibly with different mechanisms of action one tending to release serotonin at non-synaptic sites.

- *Noradrenergic* innervation of the hippocampal formation from the locus coeruleus.
  - Particularly dense in regions receiving mossy fibre input and the majority do not make conventional synapses.

Hippocampal interneurons with extrahippocampal or commissural projection

- Unconventional feature of non-principal cells
- Hilar commissural projection - there is a component of direct inhibition in the feed-forward inhibitory response evoked in the DG by commissural stimulation.
- Hippocamposeptal projection - GABAergic feedback

Post Synaptic Actions of Interneurons

- Dendrites, cell bodies, and the axon initial segment of *every principal cell* in cortical structures are innervated by inhibitory interneurons.

- Stimulation of afferent fibres elicits biphasic IPSPs in principal cells
  - first phase due to activation of (fast) $GABA_A$ receptors
  - increases the membrane conductance and therefore shunts the membrane currents
  - late phase is mediated by K^+ ion flux through channels linked by G-proteins to (slow) $GABA_B$ receptors.

- Numerous unanswered questions remain regarding how the GABA receptors are activated.

Inhibition in networks 1

- interneurons provide stability by *feedback* and *feedforward* inhibition
  - some interneurons are innervated exclusively by extrahippocampal afferents (feedforward)
  - some exclusively by inter-regional and extra-regional afferents (feedback)
  - but many are innervated by both
- recurrent inhibition is faster than the refractory period of principal cells
- feed-forward inhibition is particularly strong in the hippocampus
- there is also evidence for disinhibition
- *Boolean logic* cannot capture the rich dynamics of these networks *dynamics* (surprise surprise)

Inhibition in networks 2

- single pyramidal cell $\rightarrow$ 100s interneurons $\rightarrow$ 1000-3000 pyramidal cells
- $\Rightarrow$ *in vivo* Hippocampus with no input is quiet
- However, *in vitro* the feedback loops are weakened by behaviour via neuromodulators and neurotransmitters
- Interneurons rhythmically inhibit the pyramidal cells during θ causing their phase locked response

Role of interneurons in synaptic plasticity

- Inhibitory circuits may modify the long-term excitability of principal cells in several ways.

- GABAergic synapses on principal cells may undergo long term modifications (contrary to previous belief).

- The interneuron circuitry may be modified in a number of ways, including:
  - presynaptic changes of excitatory terminals on interneurons
  - modification of the postsynaptic sites on interneurons
  - excitability changes of interneurons
  - presynaptic modification of GABA release
  - post-synaptic GABA sensitivity changes

Interneurons shape population activity of principal cells

- Interneurons appear to be critically involved in the induction and maintenance of network oscillations in the theta ($\sim$ 10Hz), gamma (40-100Hz), and ultrafast (200Hz) frequency ranges.
- They may also regulate recruitment of principal cells during SPW bursts.
- More from Máté on this one...

Summary

- There is a(n ever growing) wealth of morphological, physiological, neurochemical data.
- This *can* be collected without regard to relevance or wider implication.
- The task of the theorist - to see the wood for the trees - is not trivial.
- It has to involve ignoring large proportions of the forest for now.