Genomic Anatomy of the Hippocampus

What is the Hippocampus?

- The Hippocampus is a major part of the limbic system – involved in long-term memory and spatial navigation.
- Codes for context – the “when” and “where” of memory (experience).

Why do we care?

No Hippocampus = Anterograde Amnesia

- Anterograde amnesia is the inability to form new memories (still able to remember things before damage, and to function in all other ways).
- The case of HM
Other Famous Cases

- EP – Discovered procedural memory (took the same test over and over again for three weeks and got better, but had no idea why... each time he thought it was the first time taking the test).
- Memento

Discovery of LTP

- Primary Messenger System (NMDA receptors 'recruit' more AMPA receptor activation)
- Secondary Messenger System – Genetic changes (New synapse structures)

How does it work?

- Entorhinal cortex -> Dentate Gyrus (DG) -> CA3 -> CA1 -> Cortex

A Conceptual Model:

- ECDG
- CA3
- CA1
- DG
- EC
- Other sensory input
- Perirhinal-Sensory components of “where”
- Perirhinal-Sensory components of object identity = “what”

How do we study it?

- Mice/Rats
- Birds

How do we study it?

- Histology – slice up the brain into fine slices and examine them under the microscope
- Nissl Stains of the hippocampus
Problems with what we know

- Different studies tend to yield different results about the how... where do these ‘memories’ go when they leave the hippocampus?
- Maybe subregions of the hippocampus can be isolated with unique functions?

Genomic Anatomy

- Brodmann’s map of cortex based on differences in cellular morphology
- By mapping out hundreds/thousands of genes, you can do even better!

Allen Brain Atlas (ABA)

In Situ Hybridization

List of In Situ Hybridization data for entire genome!

Nonnegative Matrix Factorization

Hierarchical clustering of voxel-based hippocampal gene expression data

Used a measure of expression “energy” between voxels in a data grid.

This is a way to break down huge data sets into workable amounts that you can then compare against each other.
What Happened?

NMF Data Matches our Known Anatomy!

Can we do better?

9 Subregions of CA3

Can we do better?

- Using genes that code for ‘border’ proteins (between two genes), map out boundaries for the regions.

- Identify what types of gene products are at these boundaries — Cell Adhesion Molecules (cam), ion channel regulators, and transcriptional regulators = Determine axonal growth.

3-D Models of Hippocampus

- Segregated brain into ‘voxels’ (computer generated pixels), then combined them into a 3D structure.
Retrograde Tracing
- Goes in from the synapse to the cell body

Subregions = Functionally Different?
- Layers of path-specific neurons
- If where they go is different, they should be functionally different

Conclusion
- The Hippocampus is split into 4 major areas (DG, CA1, CA3, and temporal area ~ CA2)
- CA1 and DG are uniform, but CA3 has multiple subregions. Some connect into septum.

Future Research
- Find out where they go – Determine function from the entire network.
- Learn molecular function for each of the genes
- Build a brain…