Levels of neural circuit analysis from Cajal's work

Swanson LW, Lichtman JW. 2016.
What does it take to build a brain?

• Neurons of the appropriate types must be generated in appropriate places in appropriate numbers.

• They must migrate to their final positions.

• They must differentiate into their final forms, growing out dendrites and axons.

• The axons must follow the right paths on the way to their targets, and when they get there they must recognize the right kinds of cells there with which to make contact in the right parts of the target structures.

• Finally, with all the connections approximately right (i.e., between the right kinds of cells in more or less the right places), neurons must refine their synaptic connections to a high degree of precision, keeping or finding almost all the right ones and getting rid of all the wrong ones.

• After the brain is built, it must be able to change, dramatically during early life and to a lesser extent thereafter, to accommodate growth of the organism and new behavioral or intellectual capacities.
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Acquisition of neuronal identity takes place by different means in different neurons:

Response to widespread signals

Localized signals

Intrinsic programs
Upstream signals (CoupTF1, Emx1/2, Pax6, Fgf8) in fetal life confer identity on cortical cells and determine maps.

Proof:
Ectopic expression of Fgf8 causes duplication of whisker barrel fields.

Tomomi Fukuchi-Shimogori and Elizabeth A. Grove (2001) Neocortex Patterning by the Secreted Signaling Molecule FGF8 Science 294: 1071 - 1074
Location of Some Inductive Signals in the Developing Neural Tube

- Neural crest
- Neural tube
- Ectoderm
- Somite
- Notochord
- Floorplate
- Retinoic acid
- TGF-β family
- Noggin
- Sonic hedgehog, retinoic acid, noggin, and chordin in floorplate and notochord

The Neural Crest Derivatives: 1 sensory, 2 autonomic, 3 adrenal neurosecretory, 4 non-neural (eg, melanocytes)
Cell Signaling During the Migration of Neural Crest Cells

Neural crest progenitor

Leukocyte inducing factor

FGF2

Stem cell factor

Glucocorticoids

Sensory neuron

Sympathetic progenitor

Melanocyte

Chromaffin cell progenitor

Chromaffin cell

NGF

Ciliary neurotrophic factor

Glucocorticoids

Adrenergic neuron

Cholinergic neuron

Figure 22.11 C
How do cells acquire their identities?

(A) Cell lineage model
(B) Cellular interactions model
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Regulation of cell number is poorly understood

Current hypotheses include the number of cycles of proliferative lineages (where each parent gives rise to two similar daughters producing an exponential increase in cell number) as opposed to stem cell lineages (where each parent gives rise to one differentiating daughter).

In many situations, excess cells are generated, of which only some survive after competition for neurotrophic survival factors.
Nerve Growth Factor (NGF) was the first neurotrophin.
Now we know of 3 major families of neurotrophins: NGF, Brain derived neurotrophic factor and NT-4/5, and NT-3

Figure 23.13 A
The Trk Family of Receptor Tyrosine Kinases for the Neurotrophins

Figure 23.15 A
Neurotrophins and other molecules promote survival of particular classes of neurons.

Neurotrophins secreted by the target can regulate cell number during development, matching input numbers to target.

Programmed cell death (apoptosis) is a prominent feature of the normal development of the central nervous system.
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Early neural tube cells stretch from the ventricle to the pia. Neurons are born in the ventricular zone, and migrate radially to form the cortex.
Stereotyped pattern of Cell Movements of Dividing Precursor Cells as they Progress Through the Mitotic Cycle

Figure 22.7
Radial Migration in the Developing Cortex
Radial Migration in the Developing Cortex

Figure 22.12 C
Generation of Cortical Neurons During the Gestation of a Rhesus Monkey

Figure 22.8
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Multiple molecular mechanisms regulate dendritic arborization

Figure 1 Tiling The dendrites of two dendritic arborization (da) neurons of the same class (class IV) do not overlap. The dendrites of those two neurons were colored red and green, respectively, to illustrate tiling. (Courtesy of Dr. Wes Grueber, UCSF.)
Multiple molecular mechanisms regulate dendritic arborization.
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Neuronal Growth Cone

Lamellapodium

Filopodia
• **Laminin** and **Fibronectin** are major components of the extracellular matrix (ECM).
• **Integrins** mediate attachment between the cell surface and the ECM or other cells. Integrins are very diverse, consisting of heterodimers of 18 alpha and 8 beta subunits. They may signal as well as attach.
• **Cell Adhesion Molecules (CAMs)** mediate specific forms of attachment and signaling between specific types of cells.
Floor plate cells secrete the diffusible chemoattractant **netrin**, which attracts commissural axons to grow ventrally.
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Genetic and co-culture experiments show that many neurons recognize the types of cell with which they should make connections cell-autonomously and independent of neural activity.

Cells in bits of thalamus grown over, under, or to one side of bits of cortex in the same dish, even in TTX, have specific connections to layer 4 cells.

The reeler mouse has a disorganized but inside out cortex because of a failure in migration. Nevertheless its thalamocortical and corticosubcortical and many intracortical connections are correct, despite the fact that the cells are in the wrong place. The neural circuit that is assembled in primary visual cortex gives responses with near-normal specificity.

Mutant mice without synaptic release seem to have normal anatomy.
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Chemospecific Mechanisms Cause Axons of Retinal Ganglion Cells to Project to Appropriate Positions

(A) RETINA

Dorsal

Anterior

Ventral

Posterior

TECTUM

Anterior

Posterior

(B) Normal

Rotated

Figure 23.6 A B
Chemospecific Mechanisms Cause Axons of Retinal Ganglion Cells to Project to Appropriate Positions

Temporal axons are repelled by posterior tectum

Figure 23.6 C
Chemospecific Mechanisms Cause Axons of Retinal Ganglion Cells to Project to Appropriate Positions

The repulsion of temporal axons by posterior tectum is caused by opposite gradients of Eph-A and ephrin-A. This ensures orderly maps.
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At least some maps are essentially perfect.

In the fly, the visual system maps are formed by a process resembling the growth of crystals.

Not so in the mammalian visual system, where in between the eye and the LGN, neighbor relations between axons do not persist, yet physiology shows that adult retinogeniculate connections are essentially perfect: about half are single-input RFs, and multi-input RFs are perfectly compact.
How can we reconcile this precision seen in physiology with the shaggy axonal and dendritic arbors seen by anatomy?

The apparent precision in connectivity is much better than the size of the axonal or dendritic arbors.
Precision ~ 0.1%

Precision ~ 5%, apparently
The reality is more complicated, as we are just beginning to learn from EM reconstructions, some dense as below:
And some sparse, with interesting analyses
Some steps in a connectomic analysis

1) Large scale serial section SEM of mouse visual thalamus

3) Retinal innervation of cell A

2) Seed thalamocortical cells

4) Networks of thalamocortical cells that share inputs. red = cell A

5) Mixed clusters in the dLGN network

Monosynaptic Geniculate Inputs to Simple Cells in Cat V1 from Cross Correlation
Connected Pairs
Unconnected pairs

What signal is present at the cells of origin that could be used to attain such precision of connections in the target structure?

Neural activity is such a signal.

Correlated activity of neighbors in the input array plus a reinforcement of the connections that are effective in driving the target cells can produce map refinement. Hebb's rule.
A big controversy in systems neuroscience in the early 1970s was the initial specification and the plasticity of maps, particularly that of the eye onto the optic tectum (superior colliculus) of fish and frogs (Xenopus laevis).

One side claimed that it was possible to re-specify the axes of the maps by transplantation of the eye rudiment onto the flank during a critical period in early life.

Everyone agreed that the initial map in these species could be compressed or expanded after partial lesions of eye or tectum.
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Plasticity of “whisker barrels” in primary somatosensory cortex of mouse during the first few days after birth

Critical period for “whisker barrel” plasticity in primary somatosensory cortex

Lesion of row C whisker follicles performed at postnatal ages below, serotonin transporter antibody shows thalamocortical afferents at P7-P9

There is a Critical Period for Learning Language

Figure 24.2 B

Relative fluency

Native speakers  3–7  8–10  11–16  17–39

Age of arrival (years)
Outline of Geniculocortical Visual System
Normal Cat Ocular Dominance Columns

Hata & Stryker, Science 1994
Human Ocular Dominance Columns Drawn Onto Photograph of Brain

Courtesy of Dr. Jonathan Horton, UCSF
Ocular Dominance Plasticity in the Cat

Left Visual Cortex
Upper Layers
Layer IV
Lower Layers

Right Eye
Layer A
Layer A1
Left LGN

Left Eye

Monocularly Deprived (MD)

Left Visual Cortex
Upper Layers
Layer IV
Lower Layers

Right Eye
Layer A
Layer A1
Left LGN
Monocular visual deprivation shrinks the thalamic input to the cortex from the deprived eye. This process takes only one week, and results in the loss of at least half the input.

Changes in the visual responses of input-layer (layer 4) neurons matched these anatomical changes.

The process is competitive: closing both eyes does not cause such shrinkage.
Beyond the input layer of the cortex, physiological changes in responses to the two eyes were much faster, taking only 1-2 days.

These changes have a well-defined critical period. Deprivation outside the critical period has much less effect.
Correlated activity in the two eyes is necessary to maintain binocular connections.

Ocular Dominance Histograms From Normal and Strabismic Cats

(A) Normal animals

(B) Strabismic animals

Figure 24.9
2-photon microscopy in vivo of plasticity
Correlated Activity in the developing visual system can produce changes in gene expression through calcium signaling as well as through other pathways.

Correlated activity can be detected by the flux of calcium through NMDA receptors. Remember that NMDA receptors are blocked by magnesium ions at normal resting potential. When the postsynaptic cell is depolarized, the magnesium block is relieved, and calcium then flows through the NMDA receptors when glutamate binds to them. The calcium influx then occurs only when the presynaptic cell is active at the same time as the postsynaptic cell. This calcium flux is at the head of a train of signals that lead to changes in synaptic strength and connectivity, and help to guide development.
(end of Part 1)