Neural Circuit Development Notes

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1 Thoughts

Ortus basic premise: entire system works similarly to the CO2 and O2 regulation mechanism. Aim is to keep a balance. E.g., if IFEAR goes up, this should inherently be bad. Could be that the reason for this is that it is tied to a very basic system, like breathing. So, if system is wired such that as INO2 increases, IFEAR increases, and an increase in INO2 causes an intake of O2, which decreases INO2, the system *inherently* wants to minimize INO2 and IFEAR. Everything should build off of and/or expand this basic idea/structure.

Take C. elegans, for example. It only has 302 neurons, and is a relatively simple organisim, with is connectome nearly entirely known. Despite its relative simplicity, it is capable of avoiding toxins (cite toxin avoidance), and withdrawing from a touch to the head. Both of these actions show a tendency to minimize certain conditions. In the context of an organism as simple as C. elegans, it becomes clear that this tendency arises from a circuit configuration that causes certain "pre-wired" responses to be preside over others. **This another premise of Ortus:** The idea of "emotions", as we know them, are simply the rise and fall in activation of different groups of neurons, tied to very fundamental behaviors. The concepts of "good" and "bad" sensations or emotions only carry meaning to us because of their associations to circuits that are either desirable or undesirable from a longevity perspective.

1. perhaps use a "chemical" to signal that a synapse may be be created
2. may also need to factor location in... that would be a pain, because each synapse would need a 3D coordinate.
3. classical conditioning – two stimuli paired, instrumental conditioning – stimulus -¿ response -¿ reward
4. as things get repeated, the pathway between input and output shortens (creates a "reflexive reaction", though not the same as a real reflex, like a knee jerk)
    i) **Ortus premise:** Essentially, complex behaviors are more nuanced reflexes. A reflex goes from a sensory neuron to the spinal cord where interneurons redirect the signal to a motorneuron. Complex behaviors originate from some combination of existing neural activity and sensory input, which combine and, after being passed through a number of different interneurons, end up as signals to motor neurons, or loop back around to continue the "thought" process.
5. Should have a loop that re–energizes (in a decaying way) neural pathways/circuits that were recently used. In this way, perhaps we can implement instrumental learning, and time–based/sequence–based knowledge.
6. rodent and human brain have same basic structure, it seems. things tend to be organized fairly similarly, relative to each other. 33.2
7. 33.2 are discussing rodent experiments that cause lesions to regions of the brain, so ortus should be able to function by using single neurons to represent groups of neurons, while there isn't a requirement for greater behavioral nuance.
8. What if the inherent connections we have are the only ones that just 'grow', and the only way to grow new synapses from experiences/life is something similar to the "triangle inequality"

   i) If A fires, and B fires, and C fires, and A has a CS with B, and B has a CS with C, then we create a synapse between A and C.
   ii) For GJs, if A fires, and D fires, and at the same time, B fires and C fires, and A has a CS with D, and B has a CS with C, then we can create a GJ between C and D.

9. might make sense to have different "genes" responsible for excitatory and inhibitory synapses

10. problem with worm was we would need to get too specific, and that doesn't necessarily help with generalized AI. For that goal, it makes sense to look at specific things, but then to figure out how to map that to a more generalized approach—e.g., map the concept of "genes" to something pluggable/switchable that can help shape a connectome.

    i) essentially, virtual DNA.
       a) InstructionUnits → CIU (ConnectomeInstructionUnit)

11. **Perhaps theres a chemical marker for simultaenous actions that tells the body to associate two or more sets of stimuli**

12. visual encoding (assume 16 pixels):

    i) group of 4 pixels in center, red, needs to be associated with a "touch", so some neuron gets the input from those 4 pixels, and passes that signal along to another neuron, which also gets the touch. this neuron passes that signal along.
    ii) other 4 pixels, same operation, different neuronal chain.
    iii) now, it sees both at once, so the second layer of neurons both go into a different 3rd layer (separate from the other 2 3rd layer ones that had other associations), and tie that together with some other sensory input.
    iv) the more you do this, the more intertwined your visual system becomes.

13. May need to work with space/location, but in a relative sense. A 3D coordinate may not be necessary or make sense, but perhaps each cell needs to know how close it is to other cells?

    i) might be able to use a proximity coefficient for any two neurons... problem here is we would have to either have different ones for different synapses, or assume it's okay to assign neuron to neuron PCs as opposed to synapse to synapse ones.
    ii) adjacent body parts, areas on skin, are "represented" by similarly adjacent neurons

14. locally–correlated, patterned firing

15. grow synapses with nearby neurons, maybe try reaching out probabalistically or something?

Example of CIU idea from above Not going to model cell division, too low level. But, it's clear we need a set of sensory inputs, a set of motor outputs, a set of "emotions" (including things like pain, etc in that set), and an initial set of innate behaviors. For example:

Format: if "A" then "B" which is Rule #X

1. -O2 → +MINHALE, -MEXHALE ⇒ R1

2. +CO2 → +MEXHALE, -MINHALE ⇒ R2

2 DNA, Genes, Proteins, and Cells

Genes. . .

2.1 How Genes work

https://publications.nigms.nih.gov/thenewgenetics/chapter1.html https://online.science.psu.edu/biol011_sandbox_7239/node/7260 http://genetics.thetech.org/about-genetics/how-do-genes-work

2.2 Cell Signaling

http://www.nature.com/scitable/topicpage/cell-signaling-14047077

2.3 From DNA to protein

Video: From DNA to protein - 3D https://www.youtube.com/watch?v=gG7uCskUOrA

My understanding is:

1. DNA is made up of nucleotides
2. Sections of DNA encode various genes
   i) Intergenic DNA (DNA between genes) seems to play a part in determining which genes are turned on/off, among other things. (this is part of the 98% of DNA not coding for genes)
      a) There is also DNA that sits in the middle of genes at times
         A) Exons → coding sequences, introns → intervening sequences
3. Enzymes unzip the DNA, and one side is transcribed to generate RNA—a single strand of nucleotides
   i) This happens for genes that are "turned on"
   ii) Each cell only "turns on" the genes it needs to do its job; this is due to proteins on the RNA polymerase
4. Codons are groups of 3 nucleotides, from the RNA strand, that code for amino acids
   i) There are "start" and "end" codons that mark the start and end of each gene
5. Amino acids are protein building blocks
6. The ribosomes then convert the codons from the RNA strand to proteins
   i) Prior to this, parts of the RNA are cut out during RNA splicing
      a) Exons are stitched together, using introns to dictate things like "alternative splicing"
   ii) genes are instructions for making certain proteins
7. The proteins "made" by some genes can act as switches
   i) If something goes wrong, a leg could grow instead of an antennae, for example.

a) **This suggests that as replication happens, slight changes in the expressed genes are (more or less) deterministically carried out to ensure that things like arms, legs, vertebrae, etc. grow exactly as they should**

8. Some of these proteins are receptors for neurons

   i) Some of these receptors are ligand–gated ion channels, that open to allow ions into or out of the neuron/cell.

      a) AKA ion–channel–linked receptors

      b) ligands are the neurotransmitters

3 Parts of the Brain

1. cerebral cortex (cerebrum)

   i) frontal lobe (top front) – reasoning, planning, parts of speech, movement, emotions, problem solving

   ii) parietal lobe (top middle)– movement, orientation, recognition, perception of stimuli

   iii) occipital lobe – visual processing

   iv) temporal lobe – perception and recognition of auditory stimuli, memory, and speech

2. cerebellum (little brain)

   i) associated with regulation and coordination of movement, posture, and balance

   ii) evolutionarily really old; reptiles have this as more or less their full brain

3. limbic system (emotional brain) – buried within cerebrum, like cerebellum, fairly old

   i) Thalamus - relays sensory impulses from receptors in various parts of the body to the cerebral cortex. Experts think of it as a gate. 98% of sensory input is relayed by it (not olfaction? – maybe olfaction is a more primitive sense that routes to cerebellum, and is similar to chemosensors in c. elegans?).

   ii) Hypothalamus – controls release of 8 major hormones, involved in temperature regulation, control of food and water intake, sexual behavior, daily cycles in physiological state and behavior, and mediation of emotional responses.

   iii) Amygdala – integrative center for emotions, emotional behavior, and motivation. where memory and emotions are "combined". combines many different sensory inputs.

      a) Amygdalofugal Pathway (link whereby motivation and drives can influence responses, and where responses are learned, rewards and punishments), stria terminalis (similar to fornix) – both important, come back to this.

   iv) Hippocampus – associated primarily with memory. looks like a seahorse.

4. Brain Stem – underneath limbic system, responsible for basic vital life functions such as breathing, heartbeat, and blood pressure.

   i) Midbrain – (tectum, the 'roof', and tegmentum, in front of the tectum). Tectum responsible for visual reflexes. Tegmentum coordinates sensorimotor information.

ii) Pons – connects the spinal cord to higher brain levels, and transfers info from cerebrum to cerebellum, some of which are part of the reticular formation, which regulates alertness, sleep, and wakefulness.

iii) Medulla – transmits signals between the spinal cord and higher parts of the brain, controls autonomic functions like heartbeat and respiration. Also holds part of reticular formation.

5. grey matter: pinkish–grey, contains cell bodies, dendrites, and axon terminals – so, this is where the synapses actually are. On outside of brain, but inside of spinal cord.

6. white matter: axons, which are connecting the different parts of grey matter to each other. On inside of brain, but outside of spinal cord.

So, basically, input goes into thalamus, and is then relayed, in this way, associations can be built. Thalamus has three groups of cells:

1. Sensory relay nuclei – These include the ventral posterior nucleus and lateral and medial geniculate body. Relay primary sensations by passing specific sensory information to the corresponding cortical area.

2. Association nuclei – receive input from specific areas of the cortex, which is projected back to the cortex to "somewhat" generalized association areas, where they regulate activity.

3. non–specific nuclei (intralaminar and midline thalamic), which receive input from cerebral cortex and project information diffusely through it. Most of these interconnect brain activity between different areas of the brain and play a role in general functions such as alerting.

Note: brain part info from

1. http://www.news-medical.net/health/What-does-the-Thalamus-do.aspx

2. http://neuroscience.uth.tmc.edu/s4/chapter06.html – talks about fear response and amygdala

3. Britannica, and other places too...

4 Neural reuse: a fundamental organizational principle of the brain. [1]

Test...

5 Functional roles of short-term synaptic plasticity with an emphasis on inhibition [2]

Test...

6 Emerging roles of astrocytes in neural circuit development. [3]

Test...

7 Synapse Formation in Developing Neural Circuits [4]

Test...

8 Astrocytes: Orchestrating synaptic plasticity? [5]

Test...

9 Two matrix metalloproteinase classes reciprocally regulate synaptogenesis [6]

Test...

10 Neural circuits on a chip [7]

Test...

11 Understanding synaptogenesis and functional connectome in C. elegans by imaging technology [8]

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12 Single-Cell Memory Regulates a Neural Circuit for Sensory Behavior [9]

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13 Neural circuit rewiring: insights from DD synapse remodeling. [10]

Test...

14 Rules for shaping neural connections in the developing brain [11]

Review article, proposes a detailed set of cellular rules that govern activity-dependent circuit refinement. Synthesizes what has been learned in the extensive experimental lit. on the dev. of the visual system. (strong emphasis on data obtained from live imaging of the retinotectal projection in fish and frogs). Unlike mammals, these animals rely extensively on vision for survival from very early dev. stages, and use this same visual info to direct circuit refinement.

Note: Presumably this translates to other parts of the brain, mammal or not??

1. In the contralateral optic tectum, axonal temrinals are organized such that they reconstitute a topographic map of the retina

2. Binocular projections segregate into alternating eye–specific bands in th rostral colliculus (in mammals)

3. the dorsal lateral geniculate nuclei (LGN) in the thalamus is thought to erve as the fundamental relay station through which visual information is passed to higher order cortical visual centers where increasingly complex features are extracted from visual scenes

4. the most prominent activity–dependent stages of brain circuit refinement do not necessarily take place at the same time in development (organization for different parts matures at different times), so the rules that control retinotectal refinement may be fundamentally different, or manifest themselves differently, during later refinement events.

Rules for Retinotectal Structural Plasticity

1. Molecular guidance cues provide information for coarse axonal targeting
    i) Retinal Ganglion Cell (RGC) axons will regrow to roughly the same (correct) locations after having been sectioned
    ii) Gradients of expressions of ligands cause axon attraction and repulsion, and seems to guide the path axons take
        a) Known as Sperry's "Chomaffinity Hypothesis"

2. Inputs compete for available synaptic target space
    i) It seems that relative levels of ligand expression controls the organization of a topographically ordered map.
    ii) At the single axon level, a transplanted RGC was allowed to innervate the optic tectum of a lakritz mutant fish, incapable of generating its own RGCs. The single axon was free to innervate its target in the complete absence of competition from other retinal afferents. The axon managed to target its topographically appropriate termination zone, but formed abnormally large terminal arbors. (note: they switched from singlar to pural midway though)
        a) this suggests that retinal axons do have at least a crudely defined inherent preferred termination zone within the target, presumably due to chemoaffinity cues, but that in the absence of competition for space, arbors can enlarge their coerage area (to an extent).
    iii) Seems to be more–or–less independent of neural activity
        a) reducing ability for some RGCs to fire decreases the size of arbors from those cells relative to those not restricted, however blocking all activity across the network restored normal arbor size to all cells.
            A) So, axon arbor size—important for the precision of connectivity–is regulated by activity–dependent competitive interactions

3. Axonal and dendritic arbors are highly dynaimc, even after seemingly mature morphology is attained
    i) Live imaging of axonal and dendritic remodeling in intact, transparent zebrafish and Xenopus (frog) embryos has shown that axons are perpetually extending and retracting extensive interstitial branch tips to prob the target area

ii) In zebrafish, the process by which an axon arrives at and elaborates extensive branch tips within its final terminaltion zone is not directed growth, but rather what appears to be be a process of random branch extension in which the overall progression of branch elongation and stabilization favors the future termination zone

iii) Similar in Xenopus, but individual arbors occupy a relatively larger proportion of the total tectal neuropil from earlier stages, creating a situation in which the topographic map increases in precision with age (by both restricting axonal branches to appropriate locations, and constant growth of the total retinorecipient field with age)

iv) As the tectum expands by adding cells, RGC arbors adjust and improve their relative retinotopic order by gradually shifting their positions

v) even in relativley mature tadpoles, in which RGC axons have attained their mature size and complexity, time lapse imaging still reveals ongoing remodeling and exploratory probing at branch tips (at considerably slower rates)

4. Patterened neuronal activity provides instructive cues that help refine inputs:

   i) Synchronous firing stabilizes synapses and prolongs branch lifetimes while actively suppressing branch dynamics via N–methyl D–aspartate receptor (NMDAR)–dependent retrograde signaling

   ii) Asynchronous activity weakens synapses (LTD) and actively promotes axonal branch dynamics, including addition and elongation, as well as branch elimination (Stentian mechanisms)

5. In the absence of sensory input, correlated spontaneous firing provides surrogate patterned activity

   i) dark–rearing – seems not to impact refinement of visual system, but dark rearing also doesn't necessarily deprive the visual system of all activity

   ii) in contrast to dark–rearing, using TTX to block action potential firing during optic nerge regeneration (in adult goldfish) prevented the refinement of multiunit receptive field sizes, and resulted in the degradation of precision in the anatomical projection

      a) axonal arbors were significantly enlarged

         A) in Xenopus tadpoles, blocking retinal APs led to a rapid increase in axonal branch dynamics measured as number of branches added and lost per 2 h.

      b) Locally–correlated, patterned firing in the retina, whether mediated by visual stimuli or spontaneous retinal waves, carries information about the relative locations of RGCs with respect to one another that the system can use to instruct map refinement.

6. New axonal branch tips emerge near existing synapses

7. Stronger synapses help stabilize the axons and dendrites on which they form (Synaptotropism)

8. Homeostatic mechanisms help maintain the overall level of functional synaptic input to the target

15 Correlated Synaptic Inputs Drive Dendritic Calcium Amplification and Cooperative Plasticity during Clustered Synapse Development [12]

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16 Neuronal development: Signalling synaptogenesis [13]

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17 Circuit Mechanisms of Sensorimotor Learning [14]

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18 Towards reverse engineering the brain: Modeling abstractions and simulation frameworks [15]

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19 Biologically based neural circuit modelling for the study of fear learning and extinction [16]

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20 A feedback neural circuit for calibrating aversive memory strength [17]

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21 Neurotrophin regulation of neural circuit development and function [18]

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22 Roles of glial cells in synapse development [?]

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23 Neural plasticity across the lifespan [19]

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24 The Purkinje cell as a model of synaptogenesis and synaptic specificity [20]

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25 Synapse biology in the ?circuit-age'?paths toward molecular connectomics [21]

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26 Activity-Dependent Inhibitory Synaptogenesis in Cerebellar Cultures [22]

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27 Theoretical Models of Neural Circuit Development [23]

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28 The development of cortical circuits for motion discrimination. [24]

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29 The interplay between neurons and glia in synapse development and plasticity [25]

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30 Timing Rules for Synaptic Plasticity Matched to Behavioral Function [26]

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31 Neural plasticity and behavior ??? sixty years of conceptual advances [27]

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32 Homeostatic Plasticity of Subcellular Neuronal Structures: From Inputs to Outputs [28]

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33 Mechanisms of Neural Circuit Formation [29]

(Note: this is a book comprised of research articles, title of relevant articles as subsections)

33.1 Introduction to mechanisms of neural circuit formation

Topics in book:

1. cell adhesion molecules (and downstream roles in cell identity, recognition, and synaptic specificity)

2. axon guidance, formation of terminals, and dendritic arborization

3. formation of synaptic structures themselves (remains subject to remodeling and plasticity throughout development and even in adult animals)

33.2 Wired for Behaviors: from development to function of innate limbic system circuitry, 2012

1. "Limbic system links external cues possessing emotional, social, or motivational relevance to a specified set of contextual and species–specific appropriate behavioral outputs"

2. Some enhanced through experiential learning and reinforcement, but others are innate

   i) courtship, maternal care, defense, establishment of social hierarchy → all ensure survival of individual or offspring, and thus propagation of species

   ii) regulated and influenced by sensory stimuli

3. "Emotional salience, produced in the amygdala, is generally thought of as a prime driving force behind innate human behaviors, typically social in nature"

4. This review focuses on the rodent, and because sensory inputs to rodents are primarily smell, audio, and touch, (with minimal visual inputs), the review focuses on chemosensation and how it relates to mating, maternal care, etc.

5. innate rodent behaviors, e.g.: female prefers male urine odors to female, or no odors (naive); mouse that has never encountered a predator will display signs of fear in response to predator odors.

   i) These chemicals are detected in the nose, processed by the Main and Accessory Olfactory Bulbs (MOB, AOB), projections from the AOB and MOB (directly or indirectly) synapse onto a number of higher order structures (olfactory cortex, amygdala), and the amygdala sent projections to the hypothalamus for further integration and coordination with the brain stem to initiate "fight or flight" responses.

      a) although they will focus their attention on this circuit, they state that: "we would like to emphasize that these brain hubs and their many feedback loops are not the sole components of a highly complex neural network important for the regulation of sociability an innate emotions"

6. disabling different parts of the aforementioned circuit, when looking at mating behaviors, can all have different effects on mating behavior (e.g., males seeking males)

7. defensive behaviors trigger slightly different areas of the amygdala and hypothalamus, depending upon whether the stimulus is a predator or a conspecific animal.

   i) NOTE: this seems to back up the idea of building on / expanding existing structures to grow the brain in Ortus

8. VNO organ (receptors) appear(s) to have evolved specifically to respond to cues that depend upon the animal's survival in the wild (so, to react to specific species)

9. Gene expression is correlated with "patterns to subsets of innate behaviors"

10. Estrogen and Testosterone both greatly impact (at least certain) the development of innate behaviors. In females, it is the primary hormone in the "induction of maternal care".

    i) Enzyme "aromatose" converts testosterone to estrogen in male brains. Without this, all aggressive behavior against intruder males disappears.

       a) Perhaps the hormonal state of an animal influences the connectivity? (note: that seems like it would require *very* plastic synapses. . .)

11. Hormones (sex, and others) have an impact on the formation of neural circuits as well as the modulation of innate sex–specific behaviors.

12. By embryonic day (E) 18, most neurons dedicated for the limbic system have migrated to their final locations, and in some cases, begun to make connections.

    i) Early post–natal period is primarily characterized by elaboration of both short and long range connections, and shaping of circuits via experience and sex–specific hormone levels (note: what about other hormones?)

13. Neuronal patterning and specification of neurons is accomplished via the action sof delinated sets of transcription factors (typically homeodomain and bHLH classes)

    i) These genes have been conserved through evolution and act in many specices (fly, worm, mammals) – so, they're important in neuronal dev.

14. Seems to be a genetically predetermined program of migration, differentiation, synaptogenesis, and maturation.

15. As a single olfactory sensory neuron matures, it will express a single olfactory receptor type, which detects a specific chemoical cue.

    i) During development, olfactory receptor genes are turned on synchronously in a spacially restricted manner, establishing zones.

16. Axons from olfactory receptor neurons form glomeruli (glomerulus, singular) in olfactory bulbs through a hierarchical process (olfactory sensory epithelial neurons expressing the same receptor type innervate common glomeruli)

    i) May be driven by olfactory receptor itself where a mechanism downstream of the actual olfactory receptors enables fasciculation of axons taht express simmilar receptors

       a) G–coupled receptors may generate unique level of cAMP which regulates the expression of guidance factors Nrpl and Sema3A

17. Olfactory epithelial targeting of the olfactory bulb occurs at the same time that axonal projections from the olfactory bulb to deeper brain regions occur
    i) This suggests these guidance events are independent of each other, and sensory inputs.
18. Many neuronal cell types within the brain are generated far from the mature strucutres they will eventually populate (so, it's hard to draw connections btween embryonic development and post–natal structures—this was in reference to development of amygdala and hyothalamus)
19. Different nuceli of the amygdala, associated with different behaviors, express distinct patterns of LIM–homeodomain containing genes during development.
    i) The combinatorial expression patterns of LIM genes may provide a comprehensive mechanism for patterning the amygdala
    ii) A nucleus, as it relates to neuroanatomy is a cluster of neurons that have roughly similar connections and functions
20. The same sort of gene encoding of transcription factors and regional specificity seen in the amygdala is seen in the hypothalamus.
21. Mice that don't have certain genes won't have proper positioning of certain neurons, or necessary hypothalamic nuclei (influenced by Sim1, and Otp transcription factors, respectively)
22. It's possible that in addition to patterning neuronal identity, key transcription factors encode subsets of genes (most likley cell adhesion molecules) that would be required for limbic circuit specific connectivity)
23. Gene "Met", a receptor tyrosine kinase, detected in key limbic areas (cortex, amygdala, hypothalamus, and septum, can alter arbor complexity, increase growth and excitatory synapse formation.

33.3 Protocadherins, not prototypical: a complex tale of their interactions, expression, and functions

Paper was very low–level, discusssed molecular adhesion relating to the specifics of Pcdhs—Protocadherins.

33.4 Molecular codes for neuronal individuality and cell assembly in the brain

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33.5 Synaptic clustering during development and learning: the why, when, and how

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34 Synaptogenesis: A synaptic bridge [30]

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