Neural Circuit Development Notes

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1 Ortus: Moving Forward

1. Location–based synaptic growth and decay
    i) will need to assign each neuron a 3D location
        a) initial synapse between two neurons will be midpoint between them, plus a little randomness to help ensure CSs and GJs between the same two neurons don't overlap
    ii) then each synapse will "look around" by looking at near by synapses, and either probabalistically attempting to create a synapse, or (and probably better), creating a synapse if one near by (from the same neuron) is sufficiently strong (perhaps 2 at 1/2 of the required strength would be fine too?)
        a) the speed and strength of this will decay with age... perhaps
    iii) perhaps the location of synapses formed between two neurons could be the midpoint of the two closest synapses
2. Connectome Instruction Units
3. Synaptic plasticity
    i) one way to fix the issue of needing to interact with the postsynaptic neuron and presynaptic neuron at the same time is to have a second connectome, just for writing, with modifications that should be made to the presynapses. This would be written by the postsynapses, informing the presynapse that it should increase or decrease strength.
        a) right now, the postsynapse increases the strength of the presynapse... maybe that's not an issue? The only problem with that, as I currently see it, is that there's no good way to tell the presynaptic neuron that it should "grow" new exploratory synapses near a given synapse.
            A) what about making the synapse matrix 3D, so that synapse exploration can occur based upon positive or negative change of surrounding synapses? Could probably get away with 2 or 3 "history" weights.

Initiial Goals:

1. List of CIUs in place of connectome
    i) CIUs should have rules for CS vs GJ
    ii) Build connectome using a

2. Ortus should form connectome from list of CIUs

3. ✓Innate behavior should cause a breathing cycle, lack of O2/increased CO2 should cause fear

4. Ortus should learn to fear water alone, via association with lack of O2/increased CO2

5. Ortus should learn to like water in the presence of food, while retaining fear of water in the absence of food

    i) This will require a fear center, as well as a happy center (food should cause happiness)

Why these goals?

They approximate the most basic functionality of living organisms. From there, we can expand the number of sensors via CIUs, and allow Ortus to add interneurons as needed while constructing the initial connectome. It will add neurons as it needs to in order to learn more things.

From there, the next set of goals revolve around the implementation of a very simple (e.g. 16 "pixel") visual system, that will enable ortus to "see", and associate visual stimuli with emotion. After the "Initital Goals", during which we will have added fear and happy centers, we might add anger and sad centers.

Also want to create muscles so the outputs (actions) of Ortus can be visualized.

2 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; thus, 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 organism, 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/survival perspective.

1. Perhaps use a "chemical" to signal that a synapse may be be created

2. classical conditioning – two stimuli paired, instrumental (operant) conditioning – stimulus → response → reward

3. 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) 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.

4. Maybe 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; see 14

5. rodent and human brain have same basic structure, it seems. things tend to be organized fairly similarly, relative to each other. 16.2

6. 16.2 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.

7. Is there any merit to idea of "triangle inequality"? E.g.:

   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.

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

9. 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) careful. . . don't want to go down rabbit hole.

   ii) essentially, virtual DNA (see example further down)

      a) InstructionUnits → CIU (ConnectomeInstructionUnit)

10. Perhaps theres a chemical marker for simultaneous actions that tells the body to associate two or more sets of stimuli?

11. 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 and refined your visual system becomes.

12. 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

    ii) adjacent body parts, areas on skin, are "represented" by similarly adjacent neurons

13. grow synapses with nearby neurons, maybe try reaching out probabilistically or something?

14. The fact that new axonal branch tips emerge near existing synapses means that behavior gets reinforced and things ortus repeats will become more and more ingrained... this seems to have implications for forming new memories, and working memory.

15. look into integration (signal, sensory)

16. for a sequence, you need to have a chain of neurons fire, and then that signal loops back to a sensory or inter neuron, that starts off a new chain (but slightly differently)... maybe.

17. Need to give synapses 3D location, and then we need to see which neurons have synapses within some range of that synapse.

    i) Based upon that, a new synapse can grow, and if it doesn't get reinforced, it goes away. This seems like it would be done on the presynaptic side.

18. to communicate with pre–synaptic neurons, there can be a read/write array that post–synaptic neurons can use to send "messages" to the pre–synaptic neurons on the next time–step (iteration).

19. the way to build normal associations is the same way you would go about building associations between any pair/set of stimuli.

20. GJ formation implementation is wrong; don't look for exactly lined up correlation, it should be one time–step off. Think about how the worm's muscles are connected via GJs. They don't all activate at once, they activate in succession.

21. Article talking about synaptic strength scaling with connections (more or less inversely proprotional), seems to further suggest that it's alright to model regions of the brain with one or a few neurons, and expand as necessary for more nuanced behavior.

A neuron is kind of like a person... You go out and meet 5 people. 3 of them you get along with, and 2 you don't. You end up meeting the friends of those 3 people, and maybe like a few of them, and then your network will grow/strengthen in much the same way as a neuron's axon does.

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 $\rightarrow$ +MINHALE, -MEXHALE $\Rightarrow$ R1

2. +CO2 $\rightarrow$ +MEXHALE, -MINHALE $\Rightarrow$ R2

Want to be able to show an image and do something that evokes an emotion, and then show that emotion getting evoked upon re-presentation of the image.

what if sensory neurons (maybe others, depending upon . . .) released a NT that would signal that two stimuli occurred. that would enable an association to form.

Solution to current problem could be to decrease activity of unrelated circuits, so that sensory input causes higher activation. though, breathing has to do with sensory input. . . but, potentially decreasing the threshold for certain cells, and adjusting other parameters, could help. . . There's also the idea of desensitization

3 DNA, Genes, Proteins, and Cells

3.1 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

3.2 Cell Signaling

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

3.3 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

4 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...

5 Functional roles of short-term synaptic plasticity with an emphasis on inhibition [1]

Note: paper was too high level to be immediately relevant

1. STP refers to transient activity–dependent changes in synaptic strength

i) examples include short–term depression and facilitation in the millisecond range, but also longer–lasting changes in response to highly repetitive activity, such as augmentation (lasting seconds), and post–tetanic potentiation (lasting minutes).

ii) also: adaptation/sensitization, and gain control.

2. predominantly presynaptic

   i) STP leads to stronger synaptic connections at some firing frequencies over others → conveys frequency–filtering properties

3. Adaptation and sensitization allow sensory networks to change their sensitivity and properly relay fluctuating sensory signals, can be fast or slow, and happen at the receptor level as well as higher processing centers

   i) A study investigated the effect of STP in bipolar and amacrine synapses on contrast adaptation. Some bipolar to RGC synapses depressed while a similar number facilitated. the corresponding RGCs showed adaptation or sensitization to contrast, respectively. The facilitation observed in bipolar cell synapses is caused by depression of inhibitory feedback from amacrine cells.

4. In the auditory system of birds, STP contributes to differences in the processing of different sound frequencies. Neurons in the chicken nucleus magnocellularis are organized in a tonotopic manner, and higher frequencies show less depression than lower ones.

6 Astrocytes: Orchestrating synaptic plasticity? [2]

Coming soon...

7 Single-Cell Memory Regulates a Neural Circuit for Sensory Behavior [3]

Note: I only read part of the "Results" section.

This seems suspect to me; they say that a thermosensory cell memorizes a temperature, but this is based upon cultivation temperature. While I have no doubt that the culture temperature impacts the "activation" temperature of a cell, and that non–thermosensory cells cannot sense temperature, I don't see the results discussed here as "memory". Further, I don't see how how this benefits the worm. I assume this is more of a baseline sort of thing; the worm is born, and grows, and the cell develops such that it can work within the temperature range that the worm grew up in.

8 Rules for shaping neural connections in the developing brain [4]

note: get flow chart image, figure 2, on page 12

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 terminals are organized such that they reconstitute a topographic map of the retina

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

3. the dorsal lateral geniculate nuclei (LGN) in the thalamus is thought to serve 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 singular to plural 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 coverage 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 dynamic, 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 termination 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 relatively 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. Patterned neuronal activity provides instructive cues that help refine inputs:

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 nerve 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.

iii) 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.

a) The notion of correlated firing between pre and post synaptic cells modifying synaptic strength in response to coo-activation (Hebb synapse) comes from the observation of basal occlusion by Mg^{2+} of the ion channel of NMDA receptors; which is the principal glutamate receptor type found at newly formed synapses

A) only when the dual requirements of glutamate binding and simultaneous postsynaptic depolarization to relieve the Mg^{2+} block of the pore are satisfied can the NMDAR flux current. This property of the NMDAR means that it can function as a molecular detector of correlated activity.

B) https://en.wikipedia.org/wiki/NMDA_receptor

b) blocking NMDARs with APV (which blocks the glutamate binding site) prevents refinement of retinotectal maps, meaning that NMDARs presumably act as correlation detectors.

iv) Stroboscopic rearing—producing an atypically high degree of correlation in the firing activity of RGCs—in goldfish, caused retinotectal projections to substantially overlap, and fail to refine throughout development.

a) these animals showed poor topographic refinement, with atypically large response fields.
    A) regenerating projections exhibit a similar failure to refine under conditions of stroboscopic illumination
b) individual RGCs showed long axonal arbors that were diffusely branched (rather than having formed dense clusters of branches at the temrination zone)
c) Though it seems that mice, which normally have binocular innervation of the SC, that had experienced optogenetic simultaneous co–activation of the two eye during the period of retinotectal axon ingrowth prior to eye–opening, ipsilateral eye afferent were no longer restricted to deeper tectal layers but instead appeared able to stabilize inputs within the more superficial layers where contralateral inputs normally terminate exclusively.
    A) (Note: my understanding of this, is that the stimulation impacted the growth of the axons such that they tried to account for the activation, suggesting that the correlated stimulation of both eyes caused the axons to grow as if they were coming from the same eye—in a sense) **look into this...**

v) Synchronous firing stabilizes synapses and prolongs branch lifetimes while actively suppressing branch dynamics via N–methyl D–aspartate receptor (NMDAR)–dependent retrograde signaling
    a) In order for Hebbian structural plasticity to be relevant to map refinement, postsynaptic signaling must be able to drive changes in the presynaptic axons through the production of one or more retrograde signals that can act back on the presynaptic terminal
    b) normal visual experience during the period of developmental refinement can activate postsynaptic NMDARs, and blocking NMDARs (with APV) results in a rapid upregulation of presynaptic RGC axon branch dynamics (greater number of new branch tips added and retracted) at the axon terminal.
    c) further, virally infecting postsynaptic tectal neurons, but not presynaptic RGCs with tCaMKII (a constitutively active truncated form of CaMKII, which lacks the auto–inhibitory regulatory domain, but mimics the activation of CaMKII that takes place in LTP induction), showed the expected enhancement in synaptic AMPAR currents as NMDAR–only "silent synapses" matures en masse to become AMPAR-containing functional synapses
        A) also found that RGC axon arbors grew less and had a much lower branch tip density than control cells, suggesting the existence of a retrograde signal downstream of CaMKII activation that stabilizes existing branches and suppresses branch elaboration as it drives synaptic maturation

vi) Asynchronous activity weakens synapses (LTD) and actively promotes axonal branch dynamics, including addition and elongation, as well as branch elimination (Stentian mechanisms)
    a) most retinotectal projection in Xenopus tadpoles is almost purely contralateral, occasionally one or two RGC axons end up projecting to the ipsilateral optictectum (accidentally). These end up forming synaptic contacts within the ipsilateral tectum, presumably responding to the same molecular cues that guide the contralateral RGC axons to form a crude map.

b) can test Hebbian "fire together, wire together" on these animals because the only way the lone ipsilateral RGC will fire tectal neurons is to make it fire at the same time as the contralateral inputs (so, flash light at one eye vs both eyes).

c) electrophysiological recordings showed that when both eyes were stimulated together, the ipsilateral input maintained or even slightly increased its synaptic strength relative to the contralateral inputs, but when the two eyes were stimulated 1 second apart, the ipsilateral eye input (which by itself is usually not strong enough to drive the postsynaptic neurons to fire action potentials), very rapidly declines in synaptic strength and in many cases entirely loses its ability to evoke an AMPAR–mediated postsynaptic current.

d) Asynchronous stimulation of the two eyes resulted in a rapid (within 30 min) and dramatic upregulation of new branch additions, and a significant increase in branch tip elongation compared with axon dynamics during a preceding period of darkness. Elimination of branch tips was also enhanced, indicating that rather than producing a larger arbor, asynchronous stimulation makes the axon more dynamic and exploratory (similar to the effects of the NMDAR blockade).

   A) its unlikely that the lone ipsilateral axon would by itself be able to drive sufficient depolarization of the postsynaptic tectal cell to permit Ca^{2+} flux through NMDARs, and addition of MK801 to block NMDARs did not prevent the increased rate of branch additions in response to asynchronous stimulation. It is therefore possible that the source of the branch promoting signal may not be postsynaptic in origin, but could, for example be released by surrounding glial cells, or come directly from nearby axon terminals.

e) in contrast, synchronous stimulation of the two eyes resulted in a rapid decrease in the rate of branch additions to levels seen in darkness. This decrease in branch dynamic behavior was completely prevented in the presence of MK801, or if tetanus toxin was expressed in the ipsilateral axon to render it incapable of releasing neurotransmitter.

   A) this indicates that the activation of postsynaptic NMDARs likely leads to the release of a retrograde branch suppressing factor. In addition, branches that did form during synchronous stimulation had longer lifetimes on average than those that emerged during periods of asynchronous stimulation, indicating that they were more stable overall.

f) In the normal process of activity–dependent developmental refinement, a typical axon might be expected to experience a more modest range of local correlation and asynchrony that would lead to a slight upregulation of exploratory branching and synapse disassembly on those branches that extend away from the proper termination zone (promoting them to keep growing until they land in more welcoming territory), and a stabilization and synaptic strengthening on those branches that extend into the appropriate part of the map where inputs with similar activity patterns converge (promoting consolidation and further synaptogenesis at this site). See figure 1 in paper if interested...

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

   i) "retinal waves" are patterns of spontaneous activity that exhibit a high degree of local correlation in firing, observed in the fetal retinal

ii) RGCs located in close proximity overlap their bursting activity in time, whereas RGCs that reside further away from each other are less likely to be co-active. This spaciotemporal pattern of RGC activity results from a local initiation of depolarization, which propagates to adjacent neurons, spreading over long distances across the retina.

6. New axonal branch tips emerge near existing synapses

   i) wherever a synapse strengthens (or weakens) through activity–dependent plasticity, it will be available (or not) to nucleate new branches from which new synapses can form.

      a) This constitutes a positive feedback loop that will lead to the targeted elaboration of axonal arbor at the site where that axon has formed effective, strong synaptic contacts, and the scaling back of branch initiation at inappropriate sites where synapses may form transiently but are subsequently eliminated.

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

   i) Synaptic sites are fairly labile (easily changed). The dendritic tree elaborates through a process of dynamic filopodial extensions followed rapidly by synapse formation.

   ii) As synapses form, those synapse–bearing branches become consolidated, and further branch extension then proceeds by building upon those more stable sites.

      a) blocking neurexin/neuroligin signaling or AMPAR trafficking (in Xenopus) tectal neurons prevents synaptogenesis or synapse maturation (respectively)—resulting in a failure to elaborate normal complex dendritic arbors.

   iii) in zebrafish and Xenopus tadpoles, within minutes of RGC axonal branch extension, synaptophysin-GFP puncta could be observed accumulating int he wake of the advancing growth cone. Some synaptic puncta were later lost, while other became more mature over time. When these branches later attempted to retract, the presence of a mature synaptic site conferred structural stability, preventing the branch from withdrawing beyond that site.

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

   i) Both the Hebbian and Stentian mechanisms in the context of changes in synaptic efficacy are inherently unstable

      a) for Hebbian, the positive feedback loop would become unsustainable, and for Stent's extension, each time the synapse weakened, it would become less and less likely that it would strengthen again (because it would be less likely that they pre and post cells would be correlated)

   ii) The brain overcomes this inherent instability by enforcing a range of synaptic transmission within which bidirectional changes in synaptic efficacy can occur—known as "homeostatic plasticity"

      a) **look into this.**

9 Circuit Mechanisms of Sensorimotor Learning [5]

Coming soon...

10 A feedback neural circuit for calibrating aversive memory strength [6]

Coming soon...

11 Neural plasticity across the lifespan [7]

Coming soon...

12 The development of cortical circuits for motion discrimination. [8]

Coming soon...

13 The interplay between neurons and glia in synapse development and plasticity [9]

Coming soon...

14 Timing Rules for Synaptic Plasticity Matched to Behavioral Function [10]

from http://www.neuroanatomy.wisc.edu/cere/text/P4/climb.htm A single action potential from a climbing fiber elicits a burst of action potentials in the Purkinje Cells that it contacts. This burst is called a complex spike. Climbing fibers are "lazy" (but strong), thus Purkinje cells exhibit complex spikes at a rate of about 1 per second.

going to come back to this paper at some point...

1. Synaptic plasticity rules themselves can be highly specialized to match the functional requirements of a learning task
2. The fundamental requirement of associative learning is to store information about the correlations between events
    i) synaptic plasticity mechanisms have been described that can capture the correlations between coincident, or nearly coincident events
        a) **Feldman, D.E. (2012). The spike-timing dependence of plasticity. Neuron 75, 556571.**
    ii) Behavioral observations indicate the brain is also able to associate events separated in time, with requisite temporal precision
        a) During feedback–based learning, a delayed error signal must selectively modify synapses active at the specific, earlier time when the neural command leading to an error was generated
            A) known as the "temporal credit assignment" problem – think of feedback delay when throwing a ball

3. During cerebellum–dependent learning, delayed feedback about performance errors is conveyed to the cerebellum by its climbing fiber input.

    i) Each spike in a climbing fiber produces a "complex spike", and concomitant calcium influx in its Purkinje cell targets. Related pairings of climbing fiber (CF) activation with the activation of parallel fiber (PF) synapses onto the Pukinje cells result in depression of the parallel fiber–to–Purkinje cell (PF–to–PC) synapses.

        a) Thus, error signals carried by the climbing fibers are thought to sculpt away, through associate synaptic depression, PF–to–PC synapses that were active around the time that an error was generated

15 Homeostatic Plasticity of Subcellular Neuronal Structures: From Inputs to Outputs [11]

Coming soon...

16 [Book]Mechanisms of Neural Circuit Formation [12]

(Note: title of relevant articles as subsections)

16.1 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)

16.2 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 actions of delineated sets of transcription factors (typically homeodomain and bHLH classes)

    i) These genes have been conserved through evolution and act in many species (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 chemical cue.

    i) During development, olfactory receptor genes are turned on synchronously in a spatially 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 that express similar 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 structures they will eventually populate (so, it's hard to draw connections between embryonic development and post–natal structures—this was in reference to development of amygdala and hypothalamus)

19. Different nuclei 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 likely 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.

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

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

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

Test...

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

Test...

17 Gating of hippocampal activity, plasticity, and memory by entorhinal cortex long-range inhibition [13]

Coming soon...

18 Mind the Gap Junctions: The Importance of Electrical Synapses to Visual Processing [14]

Coming soon...

19 Molecular mechanisms underlying formation of long-term reward memories and extinction memories in the honeybee (Apis mellifera). [15]

Coming soon...

20 Neural Representations of Unconditioned Stimuli in Basolateral Amygdala Mediate Innate and Learned Responses [16]

Coming soon... But, from the first page "In Brief":

Neurons in the basolateral amygdala that mediate responses to intrinsically rewarding or aversive stimuli also elicit learned responses, indicating that associative learning is funneled through innate behavioral circuits to assign positive or negative emotions to neutral sensory stimuli.

Note: This is good to hear, as it seems to back up one of the main principles of Ortus.

21 Relational associative learning induces cross-modal plasticity in early visual cortex [17]

Coming soon...

22 Distinct neural mechanisms for remembering when an event occurred [18]

Coming soon...

23 Reward-Guided Learning with and without Causal Attribution [19]

Coming soon...

24 Hebbian and neuromodulatory mechanisms interact to trigger associative memory formation [20]

1. Hebbian plasticity refers to the strengthening of a presynaptic input onto a postsynaptic neuron when both pre– and post–synaptic neurons are coactive

    i) Hebbian plasticity along may not be sufficient for producing synaptic plasticity, and neuromodulatory mechanisms are also involved.

2. Auditory threat (fear) conditioning is a form of associative learning during which a neutral auditory conditioned stimulus (CS) is temporally paired with an aversive unconditioned stimulus (US) (often a mild electric shock). Following training, the auditory CS comes to elicit behavioral defense responses (such as freezing) and supporting physiological changes controlled by the autonomic nervous and endocrine systems.

    i) These conditioned responses can be used to measure the associative memory created by CS–US pairing.

3. A critical site of associative plasticity has been identified in the lateral nucleus of the amygdala (LA)

    i) LA receives convergent input from the auditory system and from aversive nociceptive circuits (note: this suggests most sensory input could become associated in much the same way)

4. Auditory inputs are potentiated during threat conditioning, possibly as a result of auditory–evoked presynaptic activity occurring convergantly and contemporaneously with strong activation of postsynaptic LA pyramidal neurons by the aversive shock.

5. Previous studies found that weak behavioral memory could be acquired by directly stimulating LA neurons, as if it were an US, when many "training" trials were used (which suggests other factors are involved to enhance Hebbian neural plasticity).

6. This study showed that activation of LA neurons during the shock period—when the activity of CS inputs and postsynaptic pyramidal neurons is correlated—was necessary for the formation of thread memories. (note: so, correlation is a necessary measure.)

    i) Also showed that disrupting correlated activity between auditory CS inputs and postsynaptic LA pyramidal neurons reduced learning–induced plasticity.

7. (somewhat unrelated to other points) CaMKII+ is a marker of pyramidal neurons, and also thought to be important in learning/memory formation.

8. They showed that activation of beta–noradrenergic receptor (β–ARs) in addition to Hebbian mechanisms is both necessary and sufficient to produce associative threat learning.

    i) Auditory stimulus, and direct activation of LA pyramidal neurons (causing correlation, as *I believe* the neurons were artificially inhibited, so a normal shock wouldn't allow the LA pyramidal neurons to fire)), while presenting a footshock (which releases NE– so, activates β–ARs), *and* microinjections of a β–AR antagonist significantly reduced learning, when compared to animals injected with only the vehicle (so, not blocking β–ARs).

    ii) Learning–induced potentiation of the CS (the auditory input) is dependent upon β–AR

        a) Note: as an aside, "Beta Blockers" are probably not good things to take...

25 Evaluation of ambiguous associations in the amygdala by learning the structure of the environment [21]

Coming soon...

26 Synaptic mechanisms of associative memory in the amygdala [22]

1. NMDA receptor antagonists prevent the acuisition of fear memory

2. Rumpel et al, 2005, used modified AMPA-type glutamate receptors to measure learning–induced synaptic potentiation in single LA neurons after fear conditioning and to examine the consequences of blocking synaptic plasticity in a subset of LA neurons on fear learning and memory.

    i) Induction of LTP drives GluR1–containing AMPARs into synapses, and preventing AMPAR delivery reduces magnitude of LTP

3. LTP is expressed through an increase in synaptic AMPARs

4. Thalamo–amygdala: the induction and expression of LTP relies primarily on postsynaptic mechanisms (thought presynaptic increases in NTs may also occur after LTP induction)

5. Cortico–amygdala: plasticity may be induced either pre or post synaptically, but is mediated primarly by increases in presynaptic NT release.

    i) Presynaptic LTP induction is mediated by a novel synaptic mechanism in which activation of presynaptic NMDA receptors on cortical terminals by thalamic afferents induces an associative and heterosynaptic LTP at the cortico–amygdala synapse.

Note: it seems like I should know this, but it's not clear to me what signal comes from the thalamus, and what signal comes from the cortical region...

27 A circuit mechanism for differentiating positive and negative associations [23]

Coming soon...

28 Neuroscience: When perceptual learning occurs [24]

"A study now finds that visual perceptual learning of complex features occurs due to enhancement of later, decision-related stages of visual processing, rather than earlier, visual encoding stages. It is suggested that strengthening of the readout of sensory information between stages may be reinforced by an implicit reward learning mechanism."

Note: Just glanced at paper, but this suggests that the approach I want to take with the visual system, having groups of neurons cluster together in effect, (described above), may be exactly what is happening in the brain.

29 Hunger Promotes Fear Extinction by Activation of an Amygdala Microcircuit. [25]

NOTE: first point backs up Ortus premises (well, at least the one about emotions driving everything, and motivations, in a sense, because very simple/fundamental motivations are a result of emotions – e.g., motivation is to not have fear, and to balance O2 and CO2; fear is obviously the emotion.)

1. Emotions, motivations, and reinforcement lare a closely related, evolutionarily–conserved phenomena maintaining the integrity of an individual and promoting survival in a natural environment.

30 Why Neurons Have Thousands of Synapses, a Theory of Sequence Memory in Neocortex [26]

Coming soon...

31 Micro-connectomics: probing the organization of neuronal networks at the cellular scale [27]

Coming soon...

32 Integrating Hebbian and homeostatic plasticity : introduction [28]

Coming soon...

33 Homeostatic plasticity mechanisms in mouse V1 [29]

Coming soon...

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34 Mechanisms underlying the formation of the amygdalar fear memory trace: A computational perspective [30]

Coming Very Soon...

35 Synaptic scaling rule preserves excitatoryinhibitory balance and salient neuronal network dynamics [31]

Coming Soon...