Structural Plasticity in the Olfactory Bulb:
The Interplay between Synaptic Plasticity and Adult Neurogenesis in Learning and Memory

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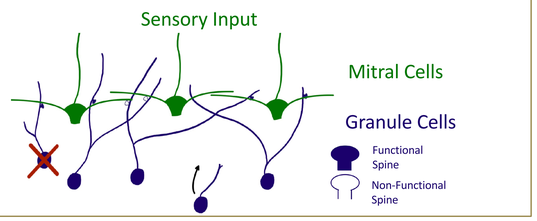
Overview: We developed a computational model of the rodent olfactory bulb and show that it provides new insights into how memories are encoded by adult-born cells and illuminates potential benefits of its two distinct forms of structural plasticity.

Introduction

The olfactory bulb (OB) is one of the few areas in the mammalian brain that undergo substantial structural changes in their neural circuitry well into adulthood. These changes, which include the formation and removal of synapses as well as the neurogenesis and apoptosis of interneurons, are presumed to play a key role in perceptual learning and forgetting. In the OB, excitatory mitral cells (MCs) form an odor representation that is shaped in part by a large population of inhibitory granule cells (GCs). Learning occurs when this odor representation is altered through network changes such as the rewiring of MC-GC connectivity or the birth and death of GCs.

Experiments have shown that:
- Adult neurogenesis is required for perceptual learning and discrimination tasks where the odors are very similar[4,5]
- Adult-born granule cells (abGCs) are preferentially recruited to process the training odors[1,2,6]
- The silencing of these abGCs extinguishes memory[1]
- Shortly after learning, abGCs are highly sensitive to retrograde interference[2]
- Increased plasticity and excitability observed in abGCs can improve spontaneous odor discrimination and improve odor coding by MCs[9]
- Spinogenesis can optimize information processing[8]
- Apoptosis is not required for initial learning[6]

Our Model:
- Informed by bulbar anatomy and properties of neurogenesis and synaptic plasticity
- Applied to perceptual learning and discrimination in the rodent OB
- Insight into contributions of these distinct forms of plasticity



Methods

- Firing rate equations for MC and GC activity :

$$\tau_M \frac{dM_i}{dt} = -M_i + [S_i - \gamma \sum_j w_{ij} G_j]_+$$

$$\tau_G \frac{dG_i}{dt} = -G_i + \alpha \sum_j w_{ji} M_j.$$

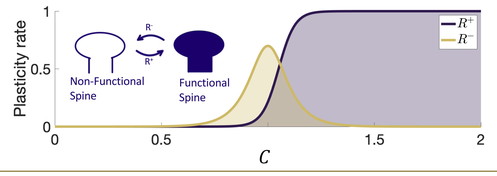
- Apoptosis:
  - Activity-dependent GC removal
  - Assume the survival rate of GCs increases monotonically with activity.
  - No significant apoptosis is observed in a control environment[7], thus we assume that apoptosis only occurs when an enrichment odor is present.
- Neurogenesis:
  - Continually add new abGCs
  - Young GCs have increased excitability, plasticity rate, and survival activity threshold as observed experimentally
- Dendritic development:
  - abGCs can only form synapses with a randomly chosen subset of MCs that is biased by the activity of the MCs during dendritic growth.
- Synaptic plasticity:
  - Driven by calcium-like variable C_{ij} at each spine satisfying (cf. [3])

$$\tau_C \frac{dC_{ij}}{dt} = -C_{ij} + c_{loc} M_i + c_{glob} G_j$$

  - large C values: consolidation (R^+) makes non-functional spines functional
  - moderate C values: deconsolidation (R^-)
  - Activity-independent spontaneous synaptic changes

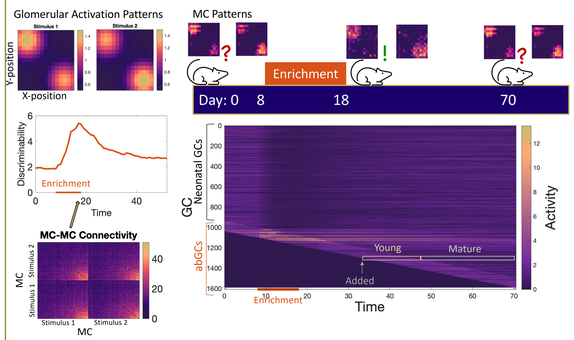
Granule Cell Development

Days 0-8 Migration to olfactory bulb | Days 8-14 Dendritic development | Days 14-28 Critical period for integration and survival



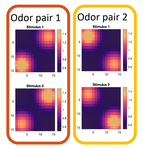
Results

Enrichment Enhances Discriminability

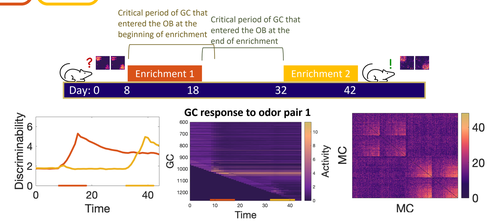


- We test the model by presenting it with two similar stimuli and observing its ability to enhance their discriminability
- Enrichment causes representation of stimuli in MC activity to become more discriminable
- MC-MC connectivity mediated by GCs: there is a dense, highly specific connectivity between MCs that are most responsive to the stimuli.
- GC activity in response to the stimuli shows that the cohort of abGCs added to the network during enrichment are specifically responsible for learning

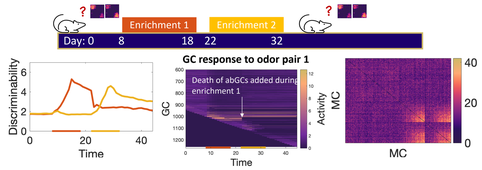
Dual Enrichment



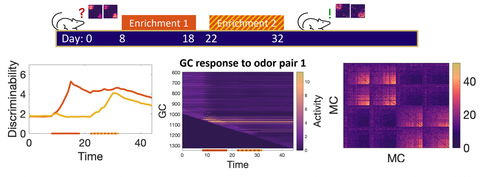
Experiment[2]:
- Well established memory persists through subsequent enrichment
- Recently learned memory is extinguished by subsequent enrichment
- Recently learned memory can be maintained with re-exposure in subsequent enrichment



As in experiments, if the second enrichment occurs a long time after the first, the memory of the first is unaffected



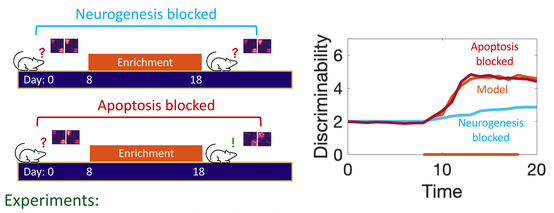
If the second enrichment overlaps with the critical period of the abGCs encoding odor pair 1, its memory is lost due to the death of these cells



If the odors from the first enrichment are present in the second, the abGCs that encode the memory of the first survive and the memory is maintained

Results

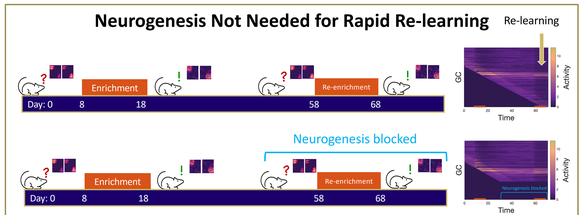
The Roles of Neurogenesis and Apoptosis in Learning



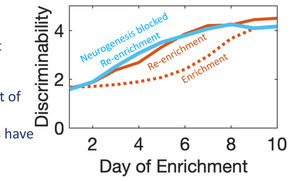
Experiments:
- Without neurogenesis, mice fail to learn during enrichment[5]
- Suppressing apoptosis makes no difference in initial learning[6]

Model:
- Blocking neurogenesis slows learning due to lack of highly plastic abGCs
- Blocking apoptosis has no effect on initial learning because apoptosis overwhelmingly removes abGCs that fail to integrate with the stimuli and thus do not contribute to learning.

Neurogenesis Not Needed for Rapid Re-learning



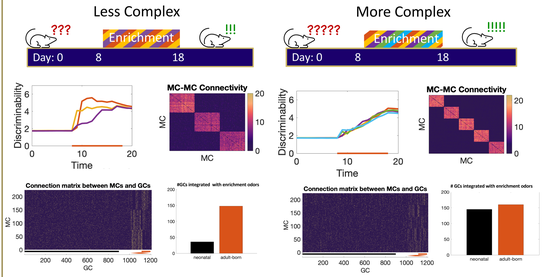
Experiment[10]:
- Mice learn faster when relearning after forgetting than during initial enrichment



Model:
- Rapid re-learning through re-recruitment of abGCs involved in initial learning
- Despite slower plasticity rate, these cells have the advantage of having dendrites near enriched MCs

Prediction:
- Rapid re-learning will occur even if neurogenesis is blocked during re-enrichment

Complex Enrichment Involves Neonatal GCs



Experiment[1]:
- Simple enrichment (single odor pair): only abGCs are required for learning
- Complex enrichment (multiple odor pairs): both adult-born and neonatal cells are required for learning

Model:
- Both adult-born and neonatal GCs are recruited to learn the odors
- With increasing complexity, more neonatal cells are recruited

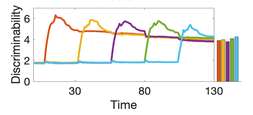
Prediction:
- GC connectivity becomes highly selective with GCs tuned to individual odorants
- Even if two sets of stimuli activate a similar number of MCs, the set with more stimuli will recruit more GCs, with more of them being neonatal GCs as abGCs are used up.

Results

Neurogenesis and Apoptosis Increase the Flexibility and Capacity of the OB

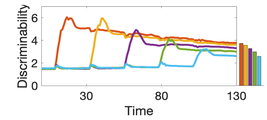
Test the stability of memories throughout sequential enrichment with multiple odors. For clarity, spontaneous synaptic changes were turned off so that memories can only change due to enrichment.

Model



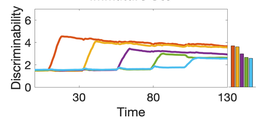
- Model learns to discriminate each pair of stimuli almost equally well
- There is little disruption in early memories caused by the formation of subsequent memories: the network learns each stimulus pair

Model without apoptosis



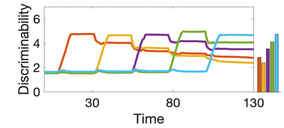
- Memories are not substantially disrupted by later enrichments
- The network eventually starts to have difficulty learning new stimuli
- Without apoptosis there is no removal of abGCs that fail to encode new information. They add nonspecific inhibition, making it more difficult for future abGCs to integrate into the network

Model without increased excitability of immature GCs



- The ability to learn decays as more abGCs are added, signaling that enhanced excitability of abGCs improves the flexibility of the network
- The transient humps in discriminability have vanished, showing that increased excitability provides a short-term boost to discrimination

Synaptic plasticity only model



- This model is comprised of only neonatal GCs with an increased plasticity rate to accomplish the same flexibility as the original model
- Each new memory partially overwrites old memories, indicating that neurogenesis may provide a mechanism to increase the capacity of the OB.

Conclusion

- Flexibility-stability tradeoff: a network of neurons must be flexible enough to quickly store new information, but it must be stable enough to prevent old memories from being overwritten
- Our model shows that adult neurogenesis, by providing young highly plastic abGCs that become less plastic with age, helps resolve this flexibility-stability tradeoff
- This supports the prediction of birthdate-dependent, odor-specific subnetworks forming in the OB as young abGCs encode new memories which then stabilize as they age while newer abGCs are recruited to form subsequent memories
- Apoptosis and the enhanced excitability of young abGCs are essential to maintaining the flexibility of the network, by helping new neurons integrate into the network in the face of otherwise ever increasing inhibition
- We further show how memories are unstable if a new enrichment occurs shortly after an initial enrichment, how re-learning a lost memory is faster than learning a new memory, and how the OB can learn several odors at the same time.

References & Acknowledgements

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