SAND2011-8840P

Adult Hippocampal Neurogenesis: Role in Learning and Memory

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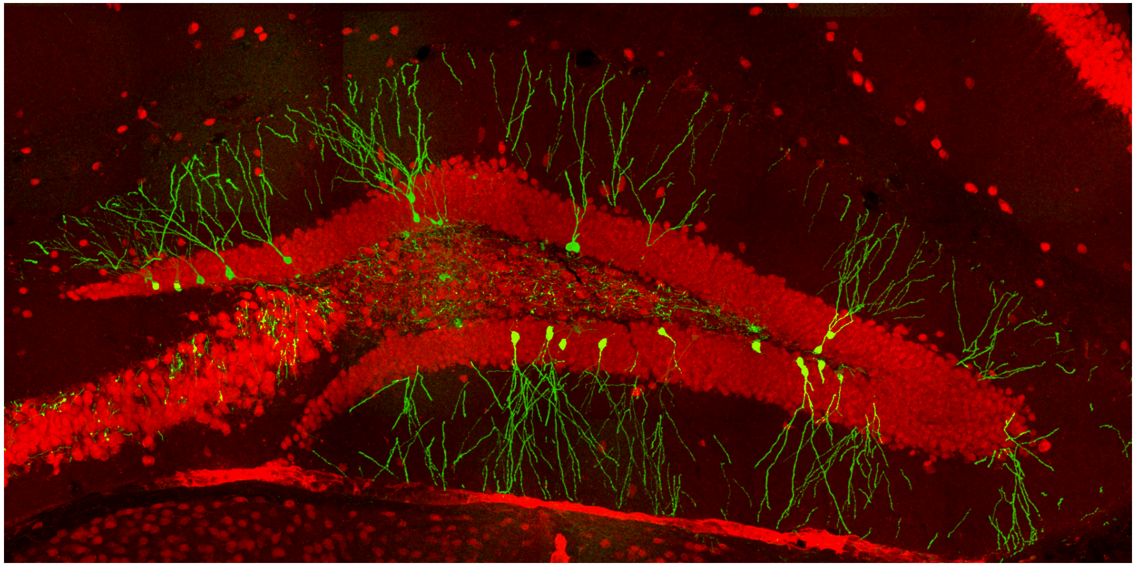
What is adult neurogenesis?

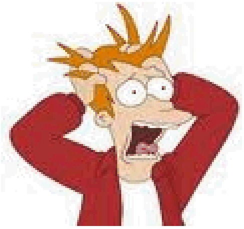
- Robust process
  - Thousands of new neurons integrate into dentate gyrus monthly



What is adult neurogenesis?

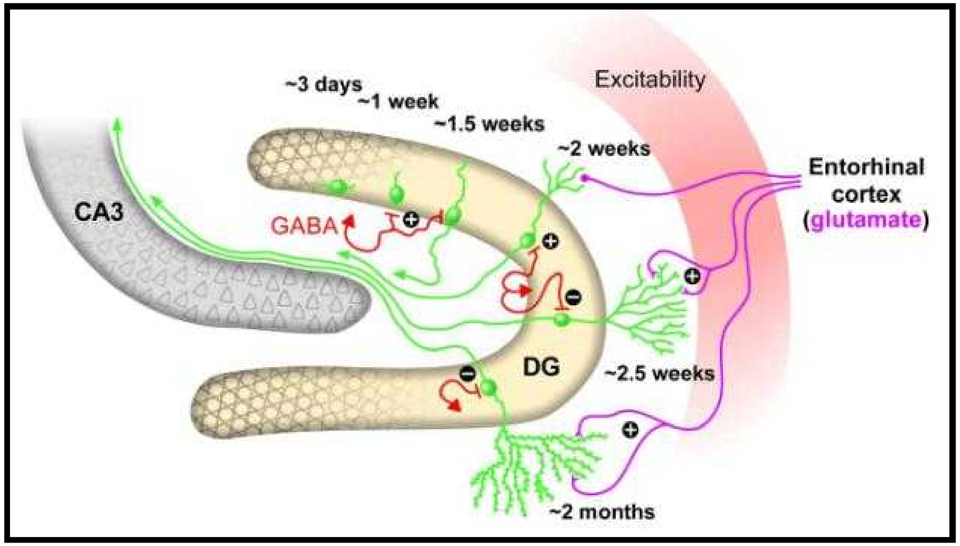
- Robust process
- Highly regulated
  - Both proliferation and survival controlled
  - Activity, enrichment, stress, diet, aging, disease…




What is adult neurogenesis?

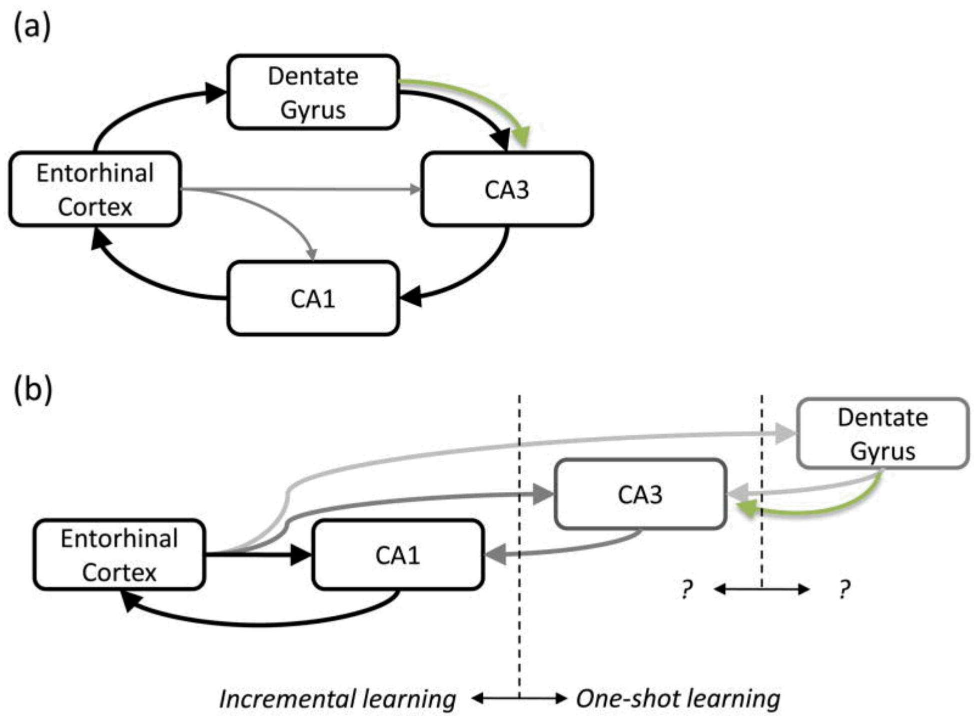
- Robust process
- Highly regulated
- Extended maturation
  - Several weeks to begin integrating into circuit
  - Still "immature" several months later



Aimone et al., Nature Neuroscience 2006

What is adult neurogenesis?

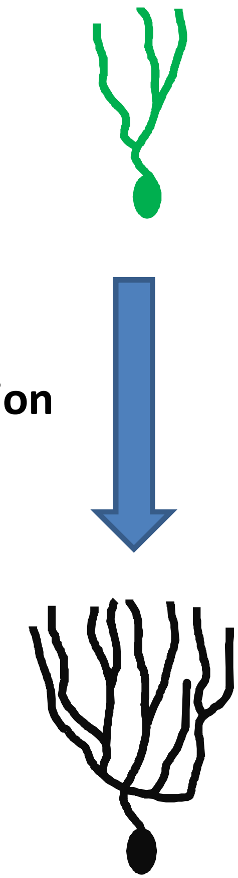
- Robust process
- Highly regulated
- Extended maturation
- Positioned to make an impact
  - Dentate gyrus is initial stage of hippocampus
  - Network amplifies effect of new neurons

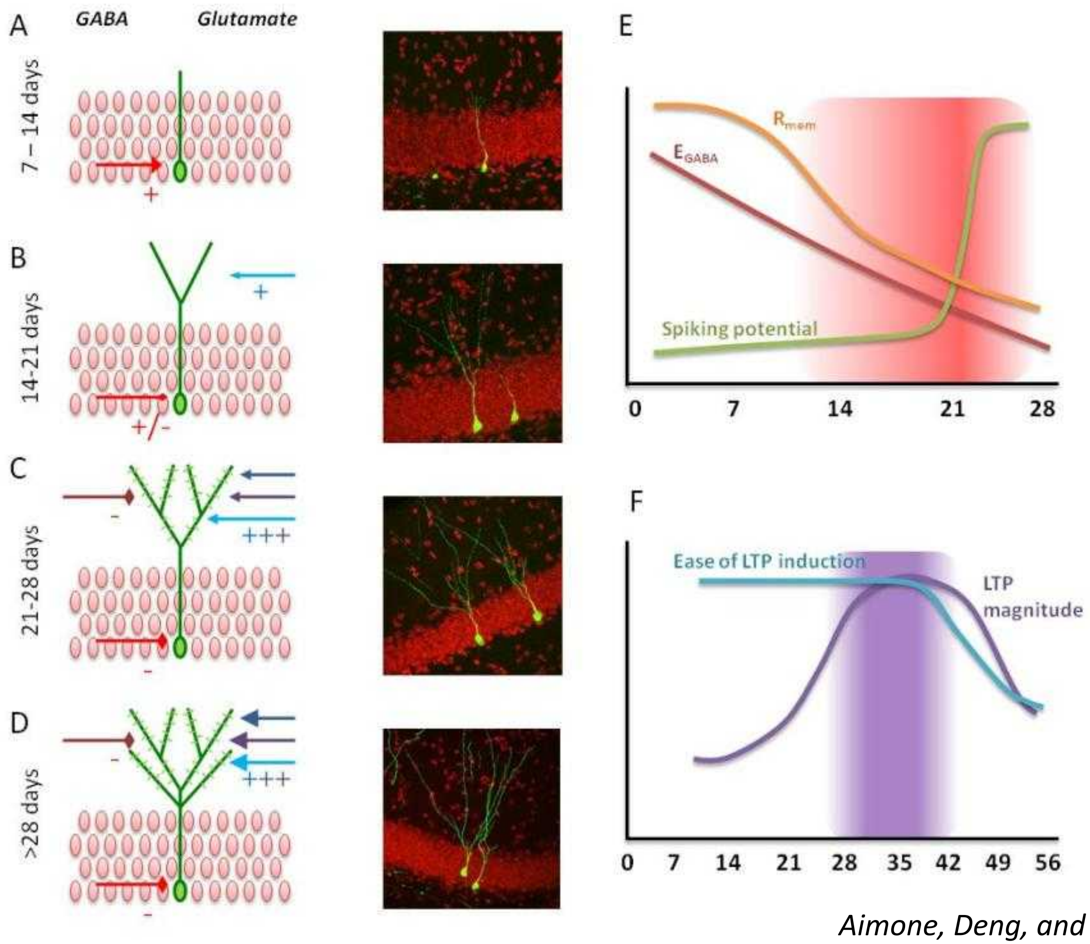


Aimone, Deng and Gage
Trends in Cog. Sci., 2010

Neurogenesis results in a mixed population of GCs

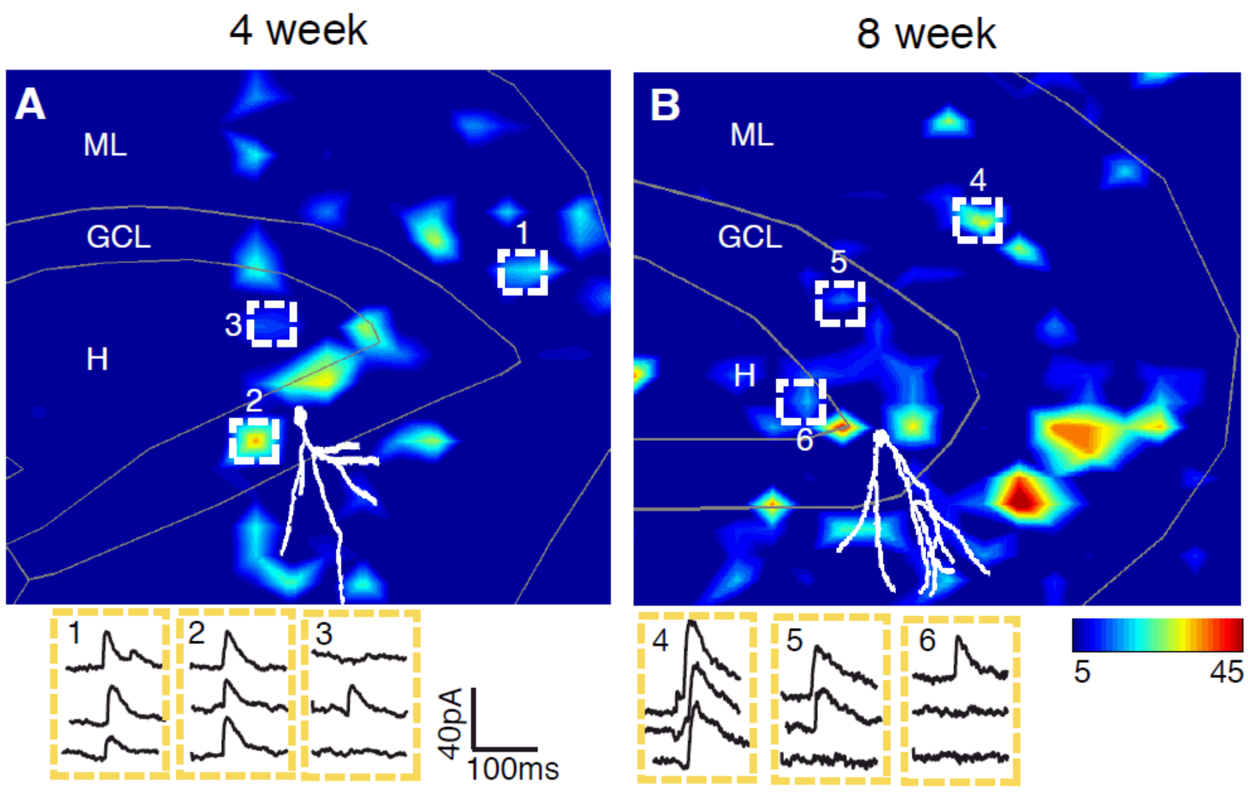
Maturation





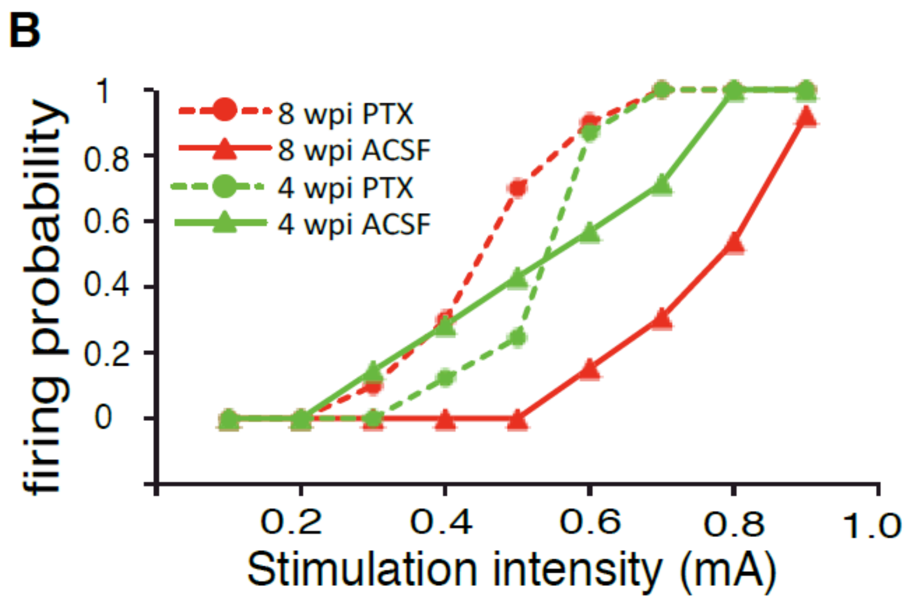
Aimone, Deng, and Gage
Trends in Cog. Sci. 2010

Inhibitory inputs onto maturing neurons



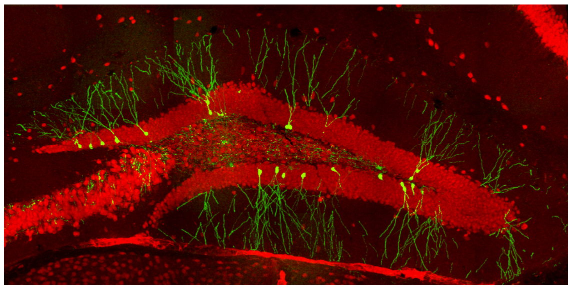
courtesy Yan Li

Inhibitory inputs onto maturing neurons

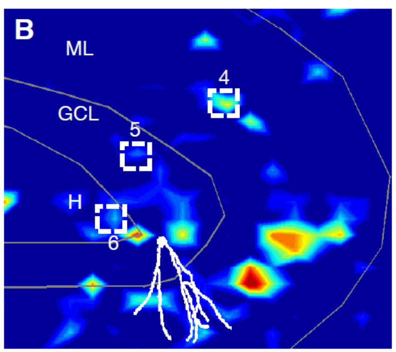


courtesy Yan Li

What are new neurons doing?



Anatomy



Physiology

Learning
Behavior

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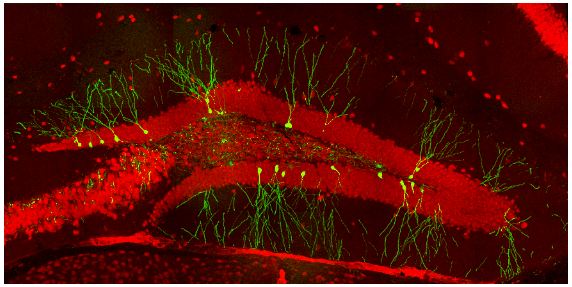
In vivo
Physiology

What are new neurons doing?



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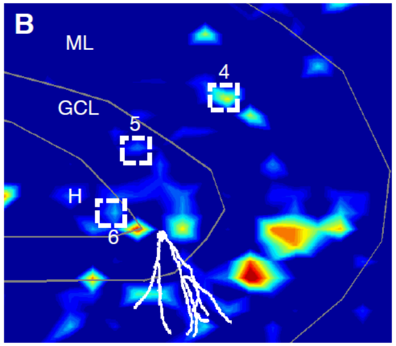

Physiology

Bottom up
Computational
Modeling

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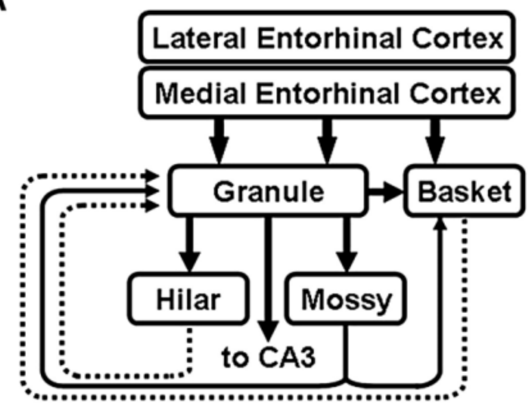
In vivo
Physiology

Modeling adult neurogenesis

- Neural network model of DG circuit

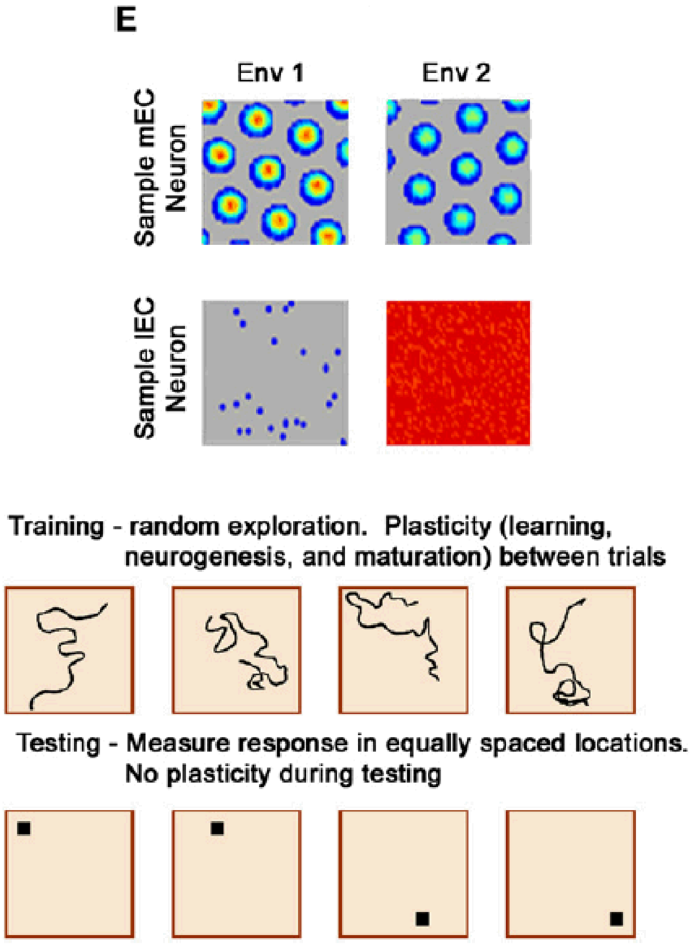
A



Aimone et al., Neuron 2009

Modeling adult neurogenesis

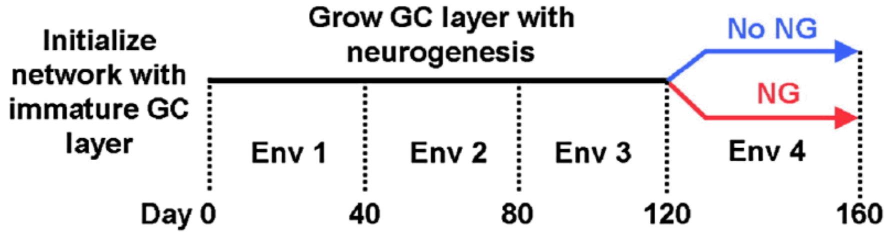
- Neural network model of DG circuit
- Biologically realistic inputs



Aimone et al., Neuron 2009

Modeling adult neurogenesis

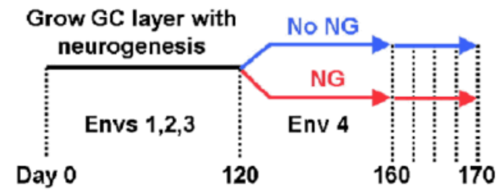
- Neural network model of DG circuit
- Biologically realistic inputs
- DG “grew” entirely through neurogenesis process



Aimone et al., Neuron 2009

Neurogenesis process allows pattern separation on temporal context

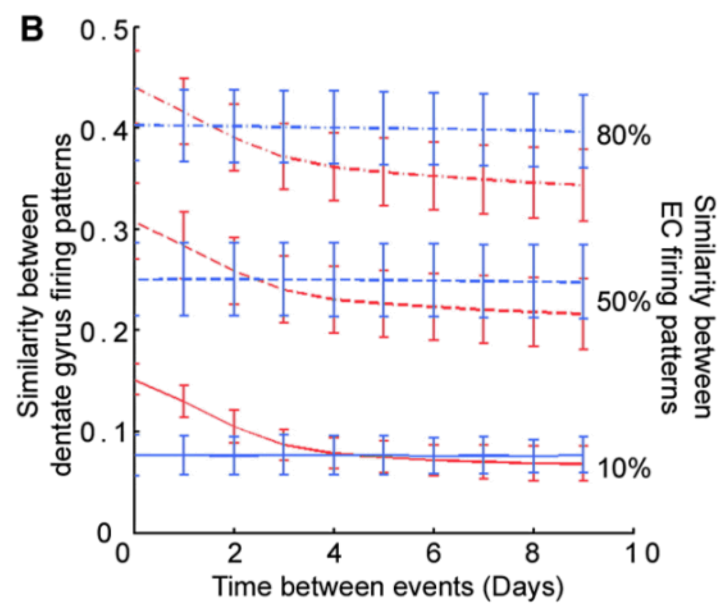
- Pattern separation between network outputs tested on different days



Measure time course of pattern separation: Compare EC & GC similarities for inputs presented at different times

- Events **close in time** activate **similar** populations of immature neurons

- Events **far apart in time** activate **different** immature neurons



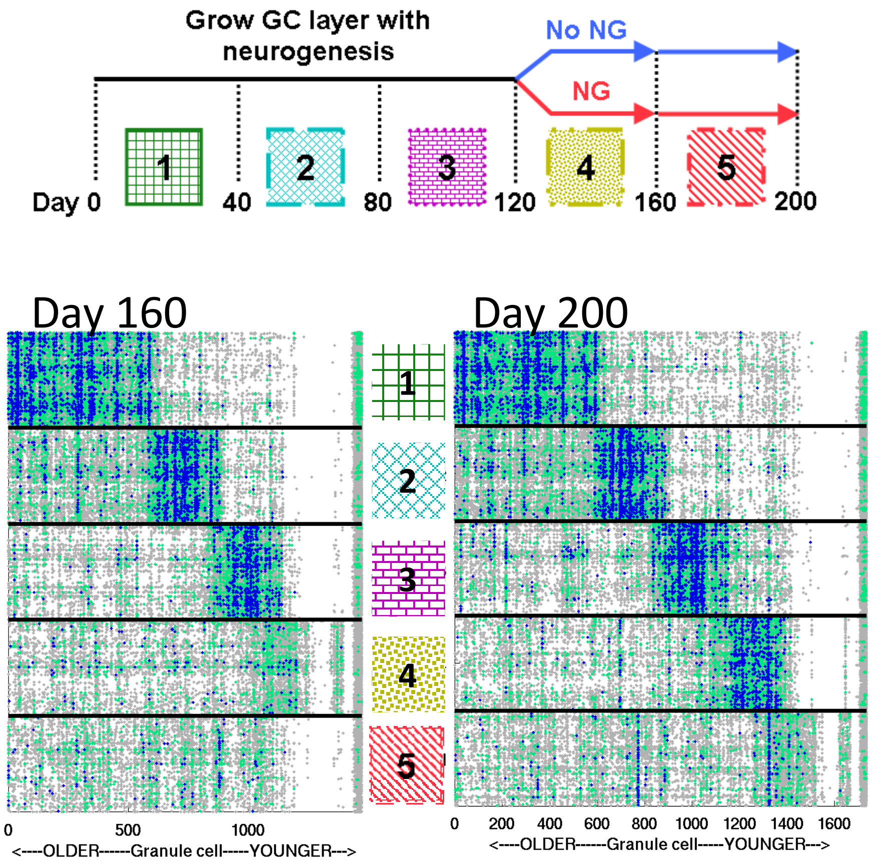
Aimone et al., Neuron 2009

Contextual specialization of adult-born neurons

- Neurons learn to represent environment present during maturation

- Prolonged exposure to environment will result in a population of DG granule cells that are “specialized” to that environment

- Networks without neurogenesis stop developing specialized groups of neurons

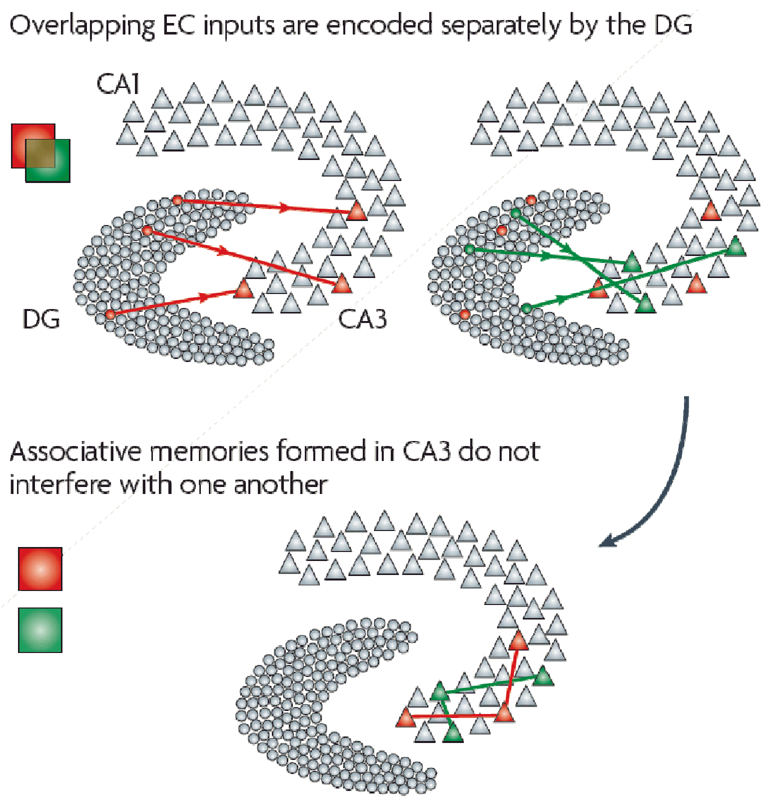


Aimone, Wiles, and Gage
Neuron 2009

Summary of model-proposed functions for adult neurogenesis

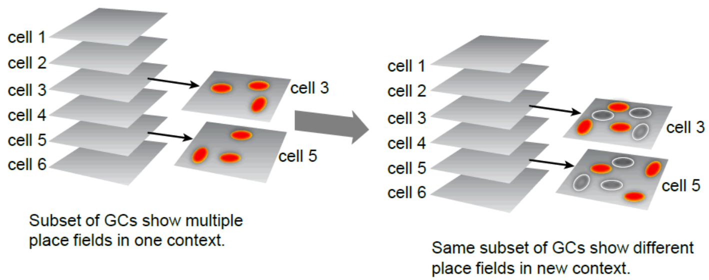
- *Pattern integration*
  - Immature neurons are indiscriminant while mature neurons separate inputs
- *Temporal pattern separation*
  - Different immature neurons are utilized for memories encoded at different times
- *Long-term specialization*
  - New neurons acquire information about environments experienced during maturation

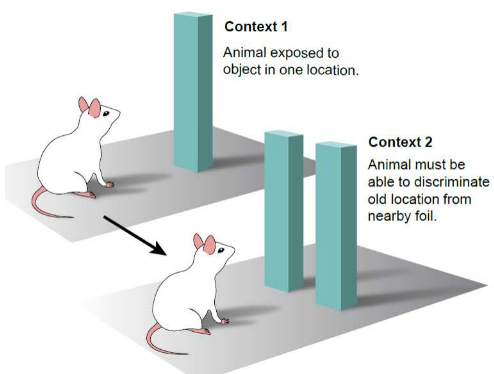
What does this mean for the DG pattern separation hypothesis?

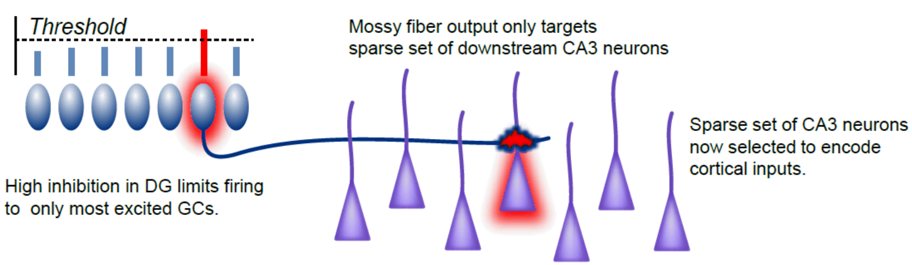


Deng, Aimone, and Gage
Nature Reviews Neuroscience; 2010

Is "pattern separation" too simple a framework?





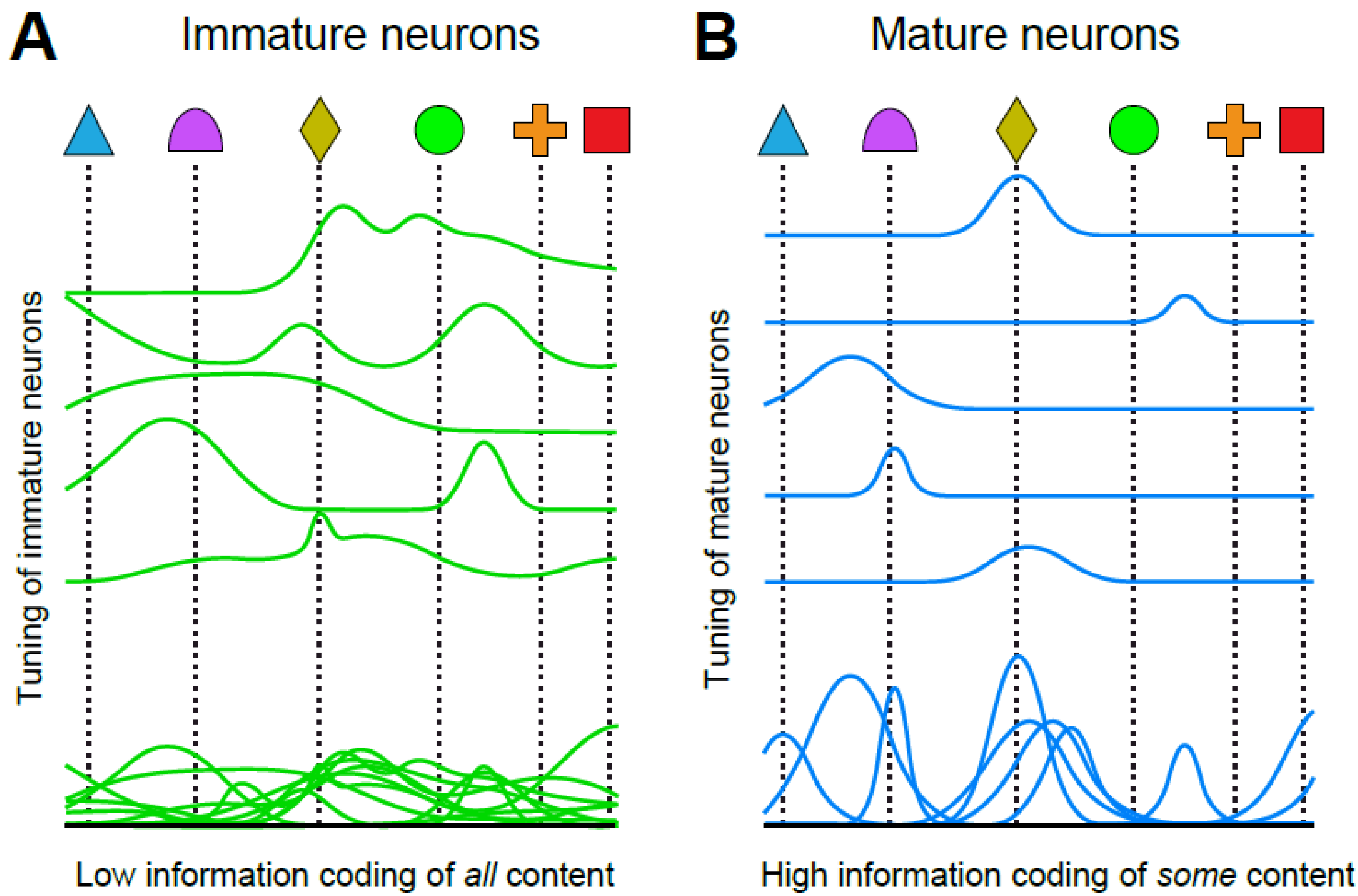


Needs to account for:

- New neurons
- Unique physiology
- Discrimination related behaviors
- Location in hippocampal circuit

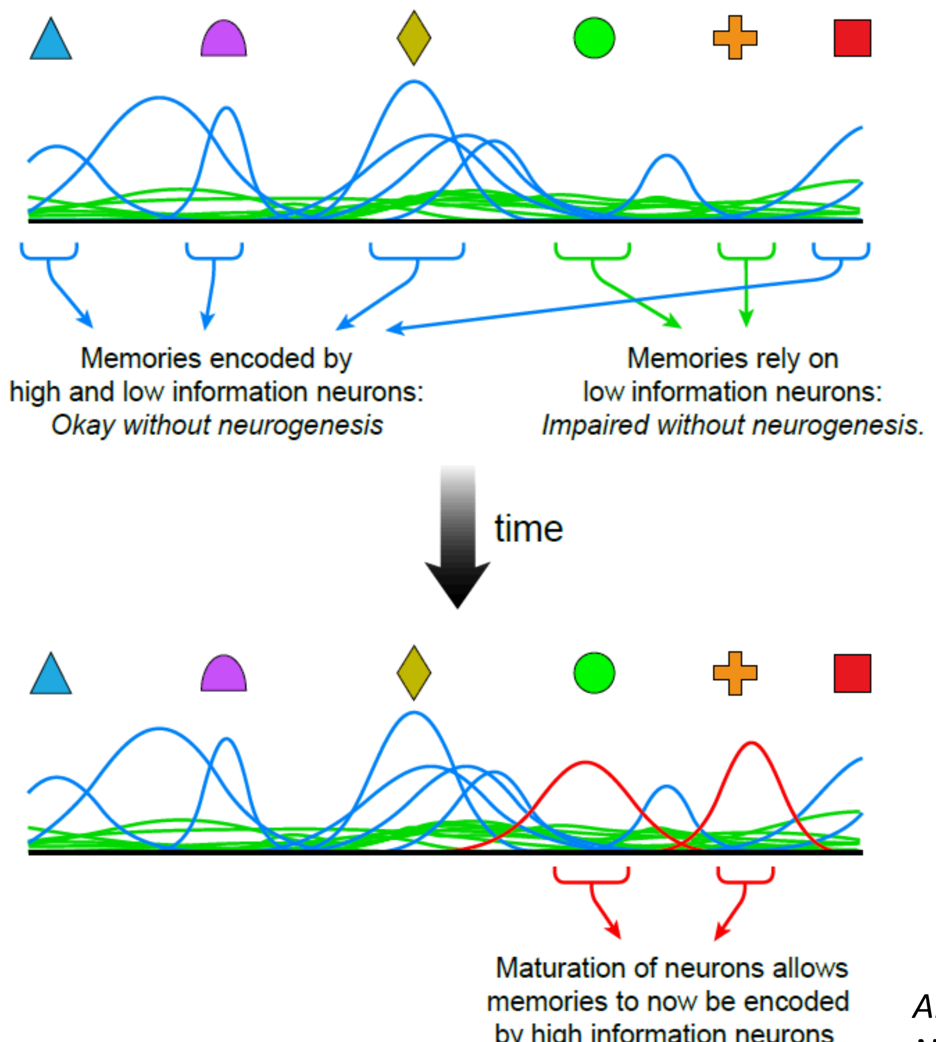
Proposal:
Memory Resolution

Immature and mature neurons encode information differently



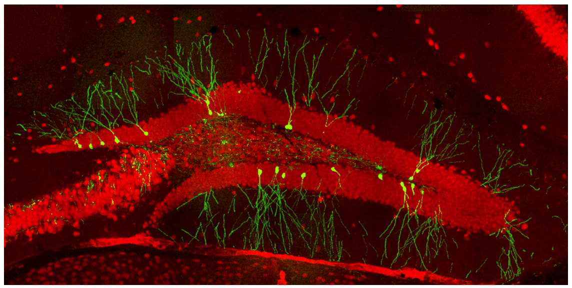
Aimone, Deng and Gage
Neuron; 2011

As neurons mature, they become high information encoders themselves

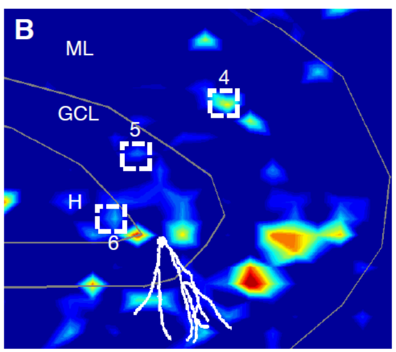


Aimone, Deng and Gage
Neuron; 2011

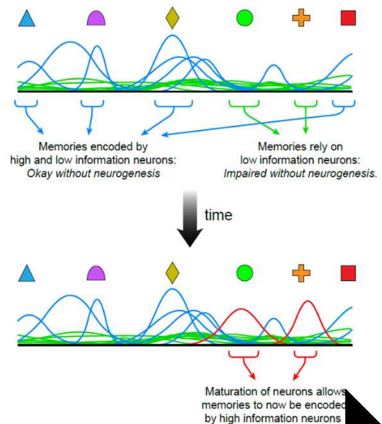
What are new neurons doing?



Anatomy



Physiology



Bottom up
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Modeling

Learning
Behavior

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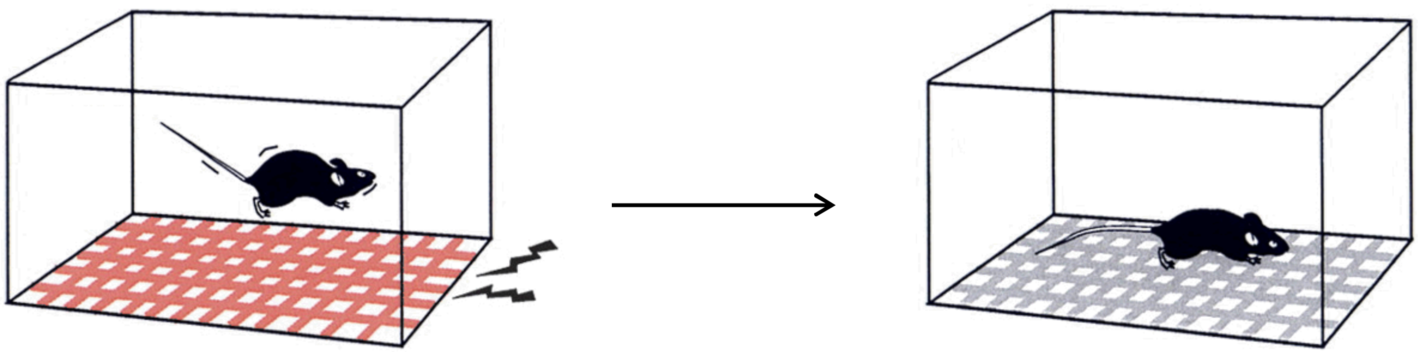
In vivo
Physiology

Contextual fear conditioning

Learning of an association between a distinctive place and an aversive event.

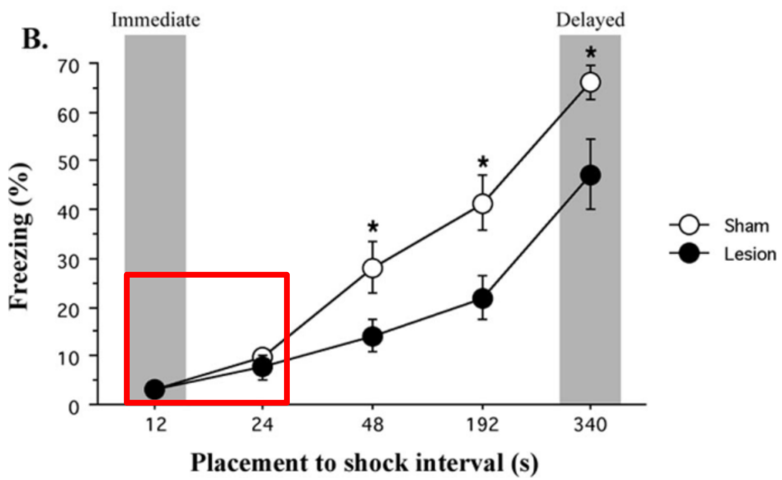


Learning of the context: indicated by freezing behavior subsequent to conditioning.
Fear extinction: less freezing subsequent to repeated contextual exposure without shock.

courtesy Wei Deng

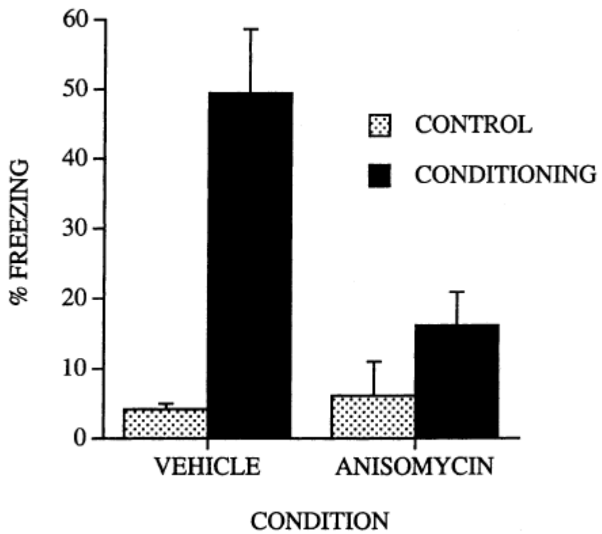
Immediate shock focuses hippocampal learning to context pre-exposure

Immediate shock deficit (ISD)



Wiltgen et al., 2006

Contextual pre-exposure facilitation



Barrientos et al., 2002

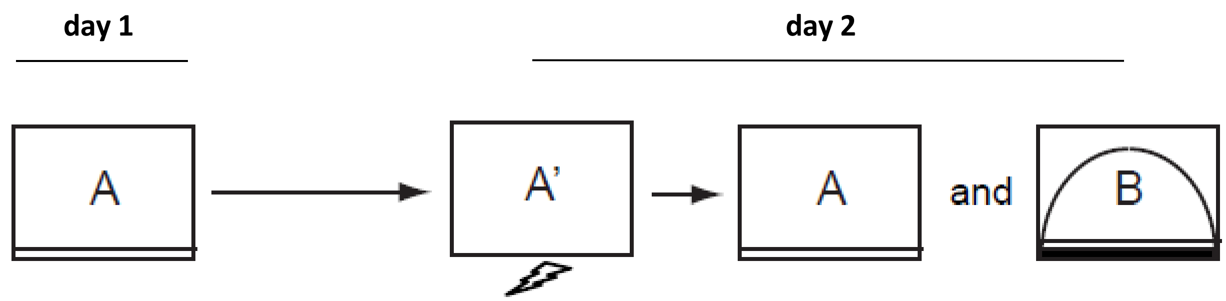
- Animals need time to explore the environment in order to associate context with the shock.

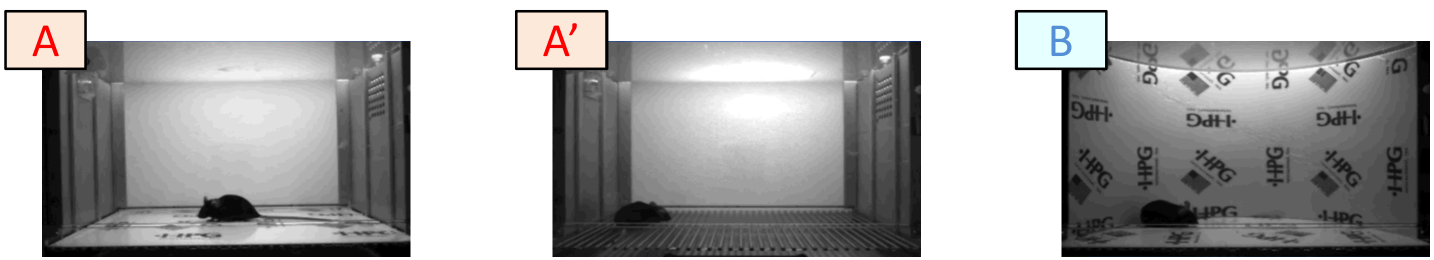
- Pre-exposure gives animals the chance to explore the chamber and thus rescues the ISD.
- The hippocampus is important for the contextual pre-exposure facilitation.

courtesy Wei Deng

An immediate shock deficit based context discrimination task

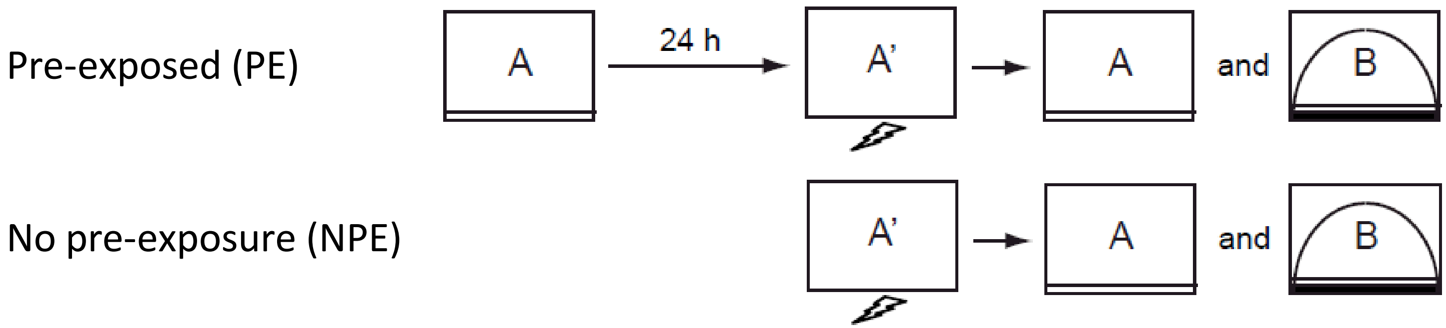
PE-ISD protocol

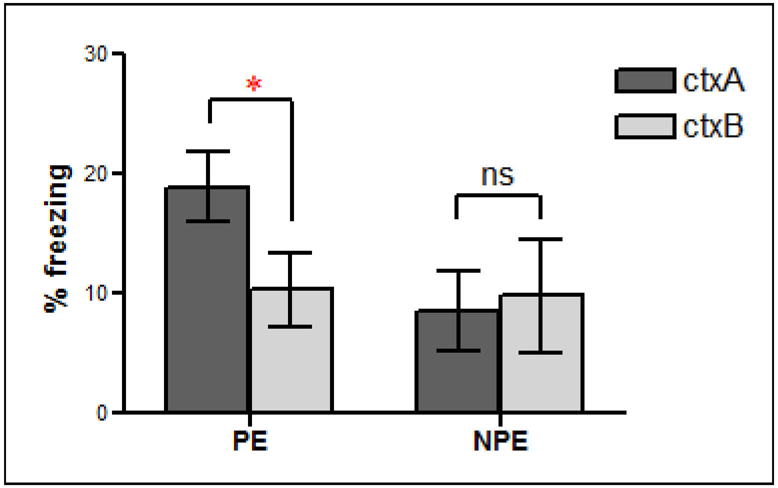




courtesy Wei Deng

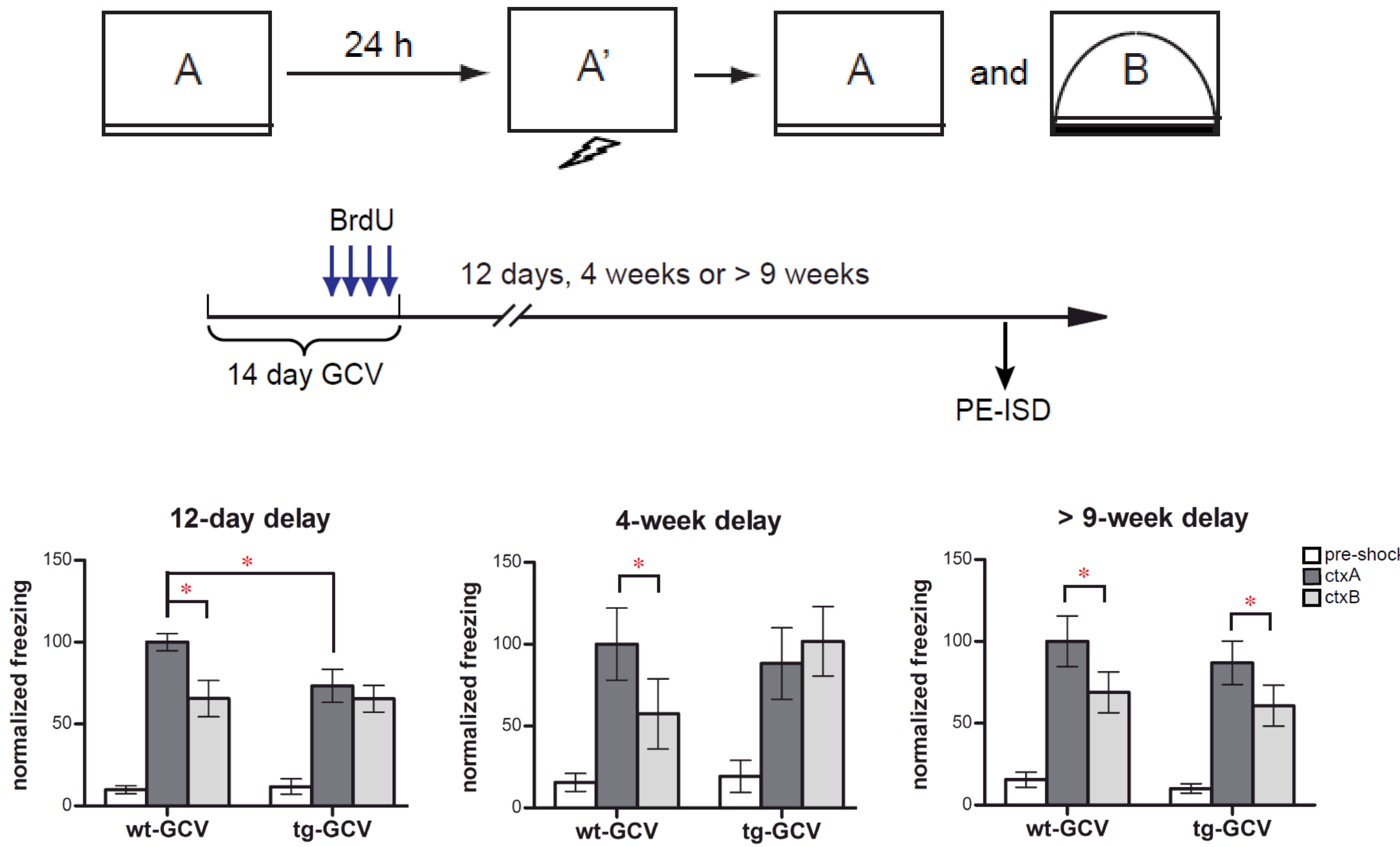
Pre-exposure is important for contextual learning and context discrimination paradigm (PE-ISD)





courtesy Wei Deng

Knocking out different populations of young neurons affects freezing behavior differently



courtesy Wei Deng

Do immature neurons specialize to temporally distinct inputs?

- Prediction: *Presenting animal with different contexts / experiences at different time should result in specialized granule cells*

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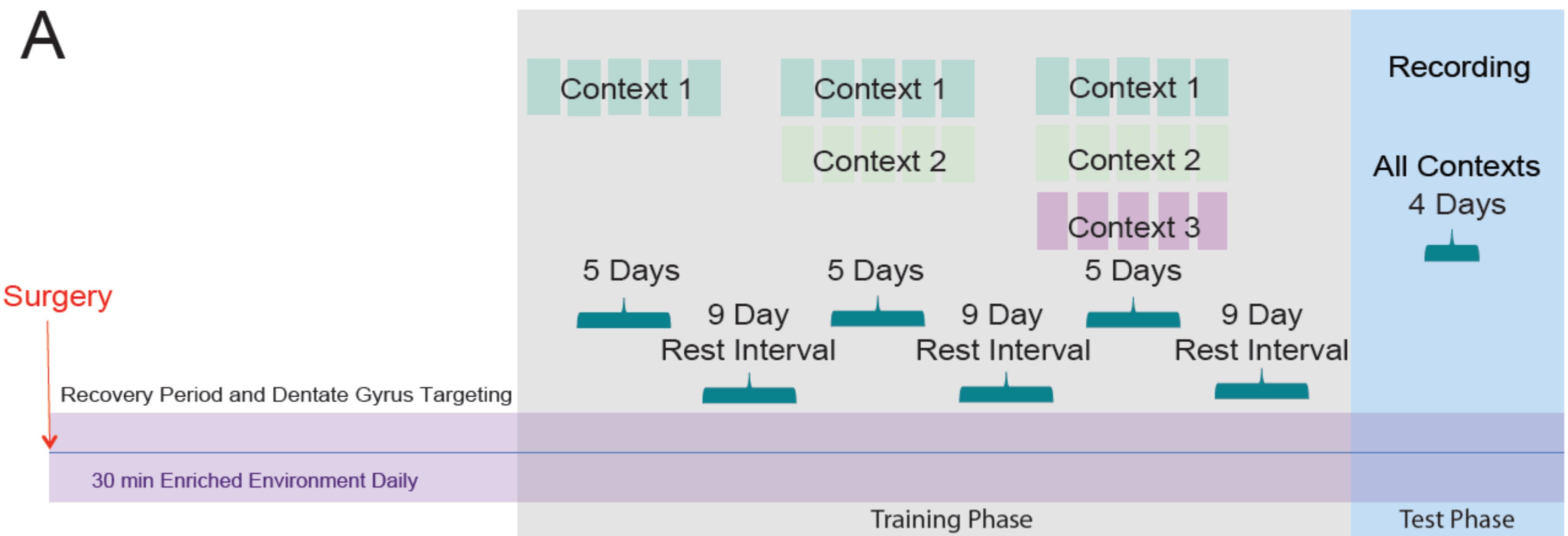
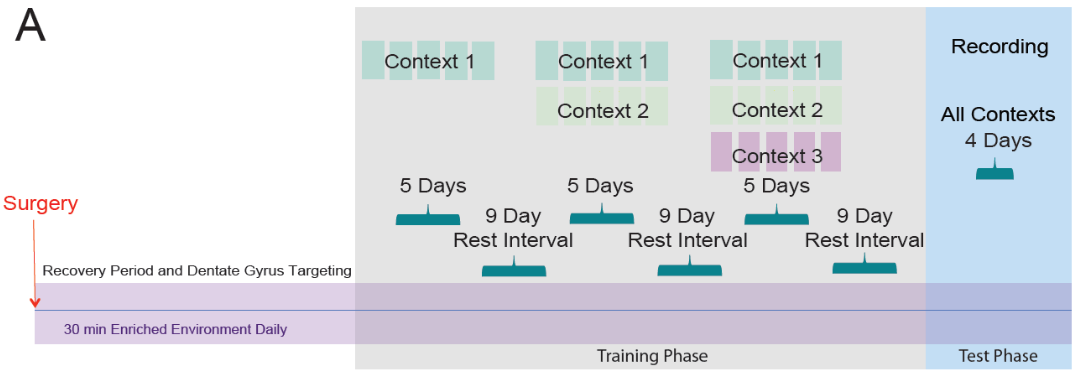
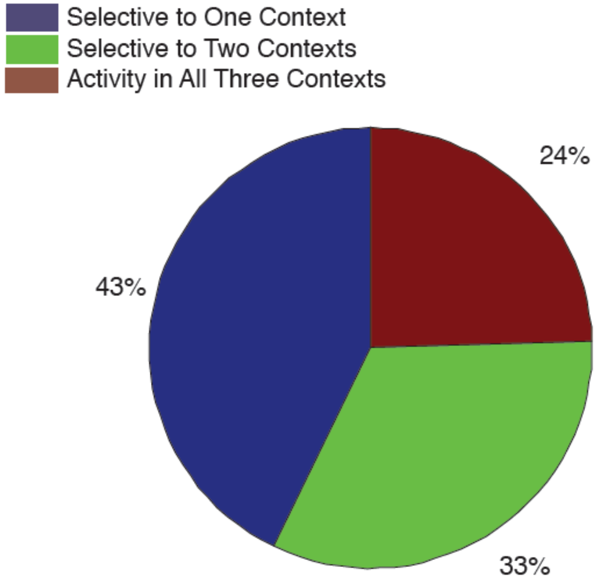


courtesy Lara Rangel and Andrea Chiba

Do immature neurons specialize to temporally distinct inputs?

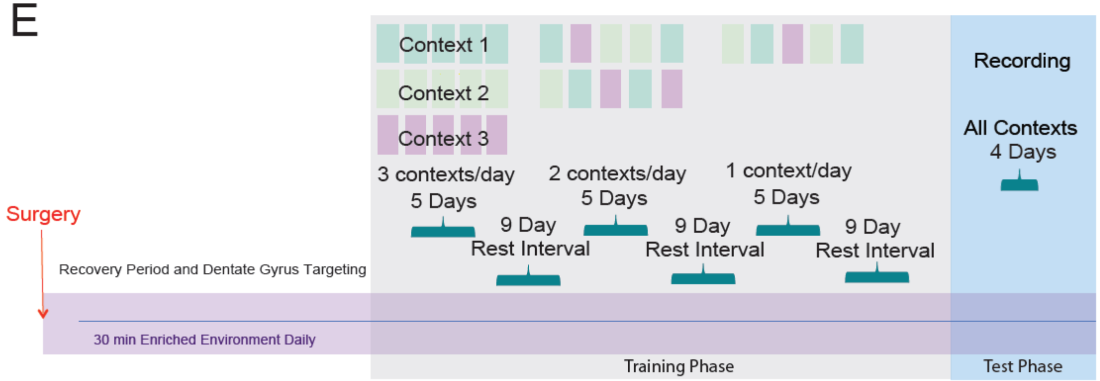


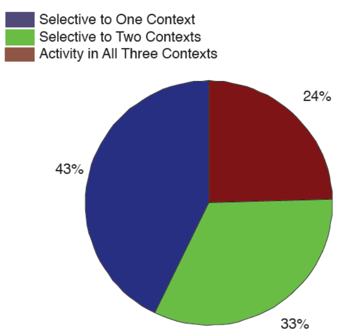


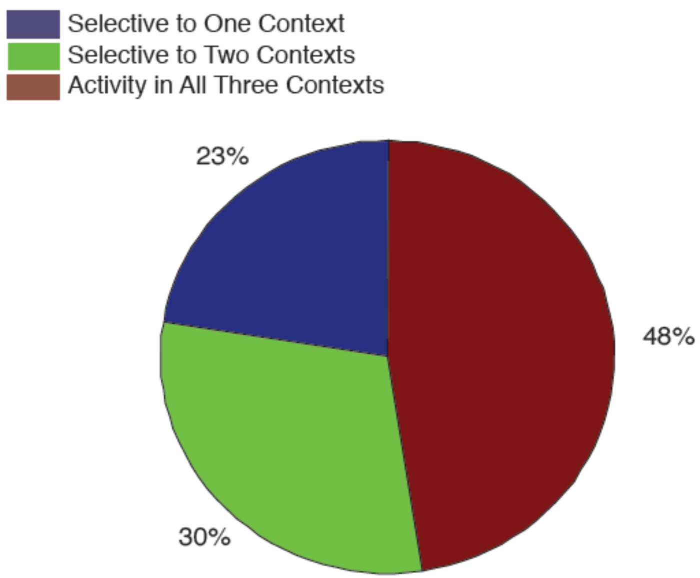
courtesy Lara Rangel and Andrea Chiba

Do immature neurons specialize to temporally random inputs?

E







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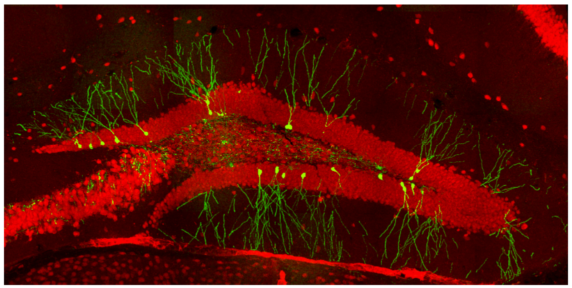
What are new neurons doing?



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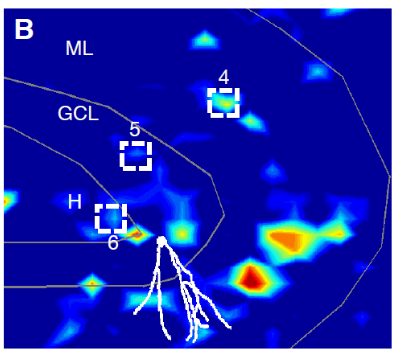
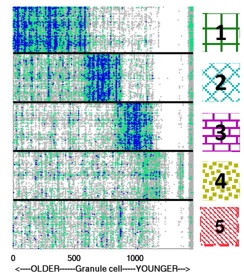
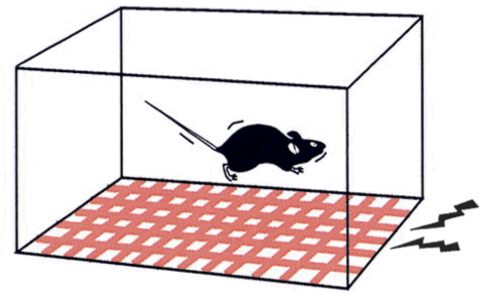


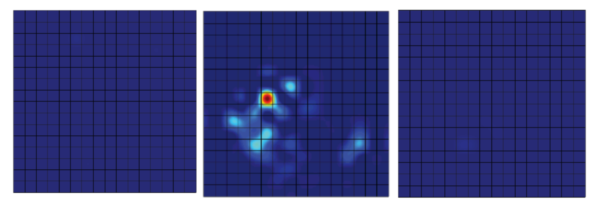
Physiology



Bottom up
Computational
Modeling



Learning
Behavior



In vivo
Physiology

Thanks!

Salk Institute

Fred Gage

Yan Li

Wei Deng

Dan Sepp

University of California San Diego

Andrea Chiba

Lara Rangel

University of Queensland

Janet Wiles

James S McDonnell Foundation

Kavli Institute for Brain and Mind

NSF Temporal Dynamics of Learning Center