SAND2013-1876P

Adult Hippocampal Neurogenesis: Memory Resolution, Pattern Separation, or Both?

Brad Aimone

Sandia National Laboratories

The dentate gyrus and hippocampus

- First layer of classic trisynaptic loop
- Essentially feed-forward network (EC -> DG -> CA3) with some local feedback

J. Physiol. (1973), **232**, *pp.* 331–356
With 12 *text-figures*
Printed in Great Britain

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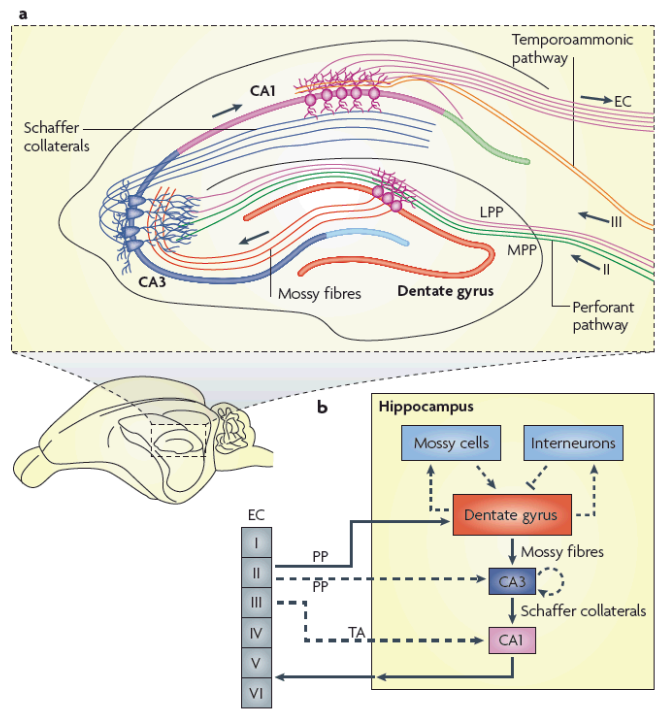
LONG-LASTING POTENTIATION OF SYNAPTIC TRANSMISSION IN THE DENTATE AREA OF THE ANAESTHETIZED RABBIT FOLLOWING STIMULATION OF THE PERFORANT PATH

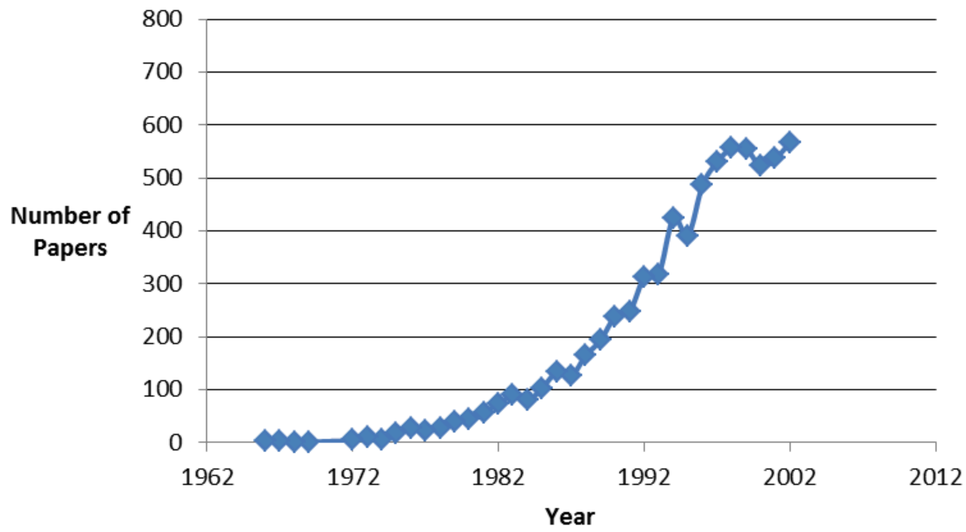
BY T. V. P. BLISS AND T. LØMO
From the National Institute for Medical Research, Mill Hill, London NW7 1AA and the Institute of Neurophysiology, University of Oslo, Norway

(*Received 12 February 1973*)



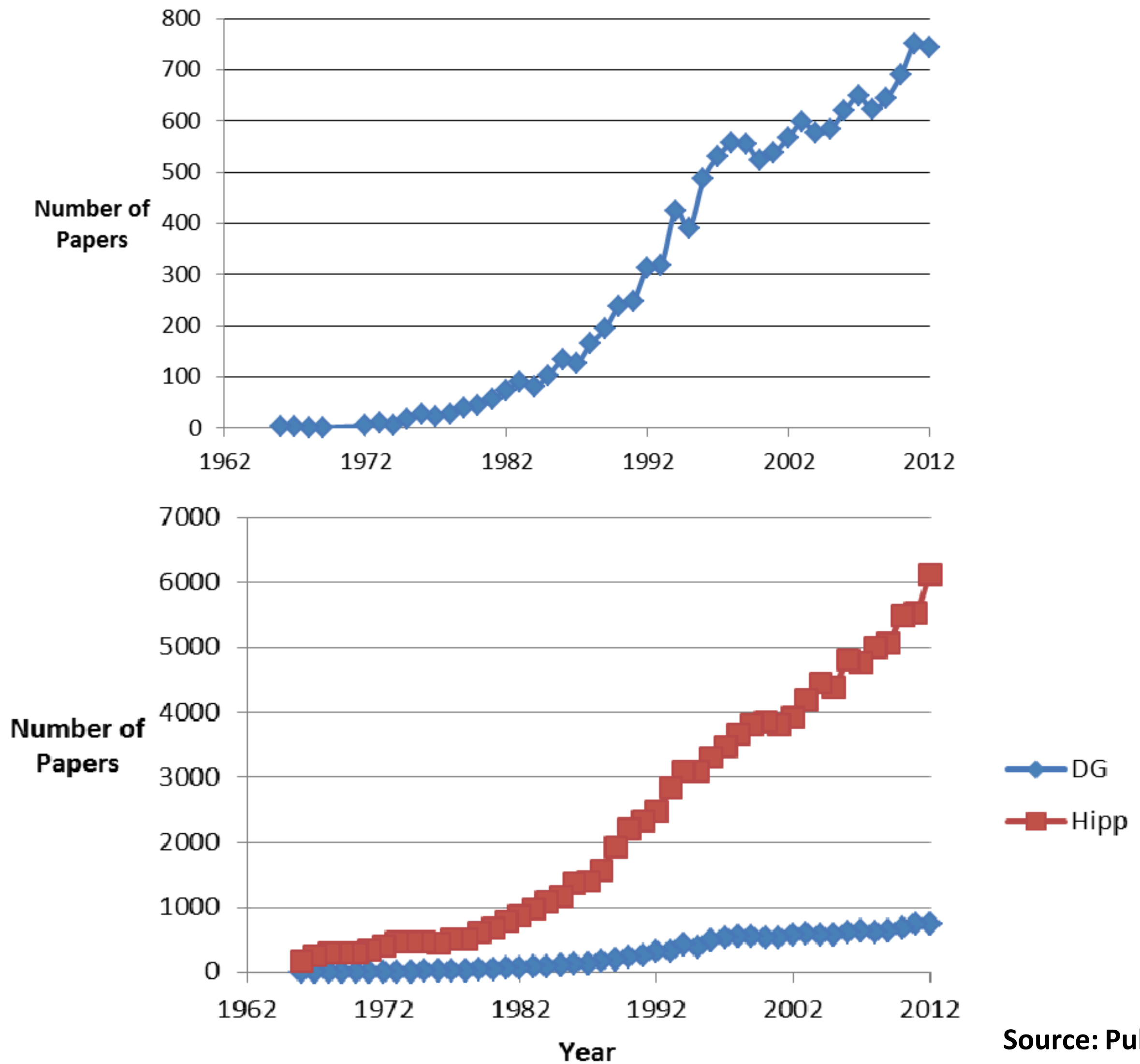
Deng, Aimone, and Gage
Nature Reviews Neuroscience; 2010

Dentate Gyrus



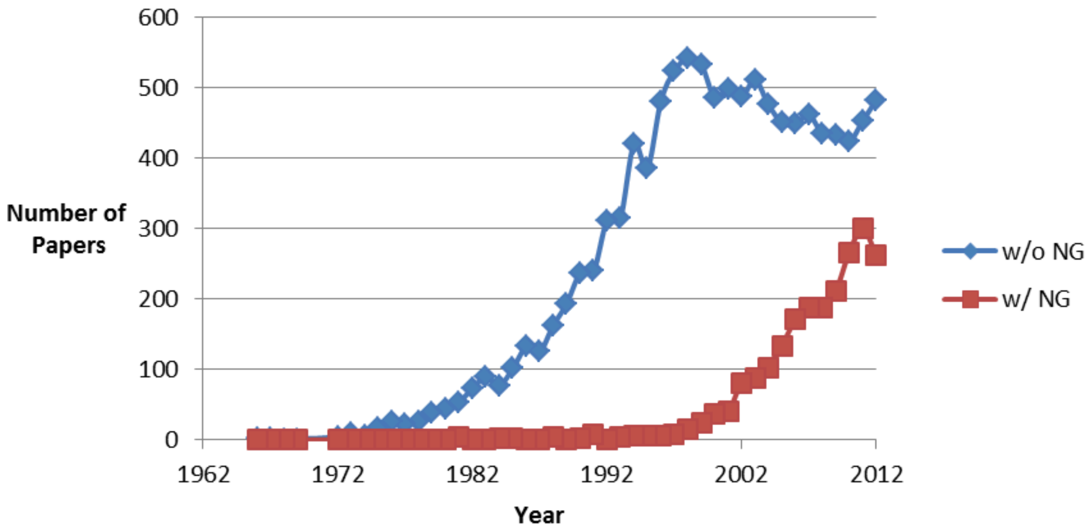
Source: Pubmed, March 4, 2013

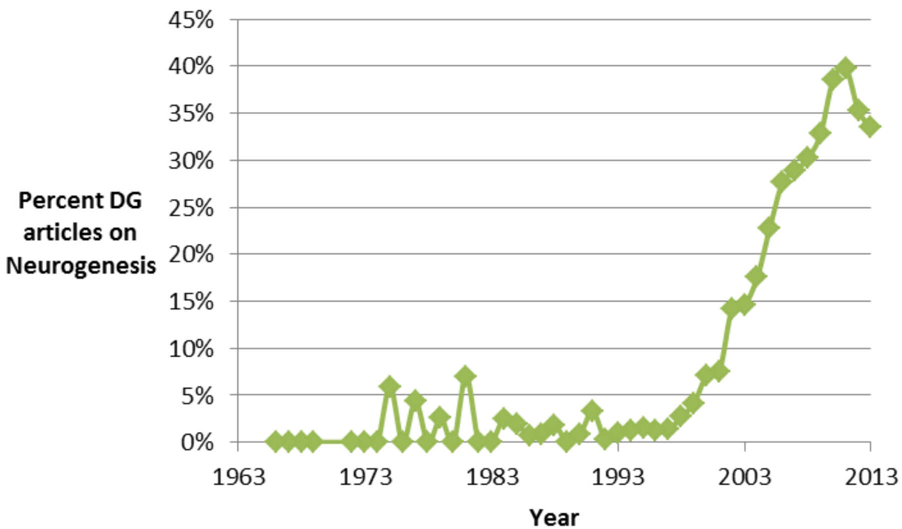
Dentate Gyrus



Source: Pubmed, March 4, 2013

New neurons





Source: Pubmed, March 4, 2013

What does the dentate gyrus do?

Neuroscience 154 (2008) 1155–1172

FOREFRONT REVIEW

WHAT IS THE MAMMALIAN DENTATE GYRUS GOOD FOR?

A. TREVES,[a,b]* A. TASHIRO,[a] M. P. WITTER[a] AND E. I. MOSER[a]

[a]*Kavli Institute for Systems Neuroscience and Centre for the Biology of Memory, Norwegian University for Science and Technology, Trondheim, Norway*

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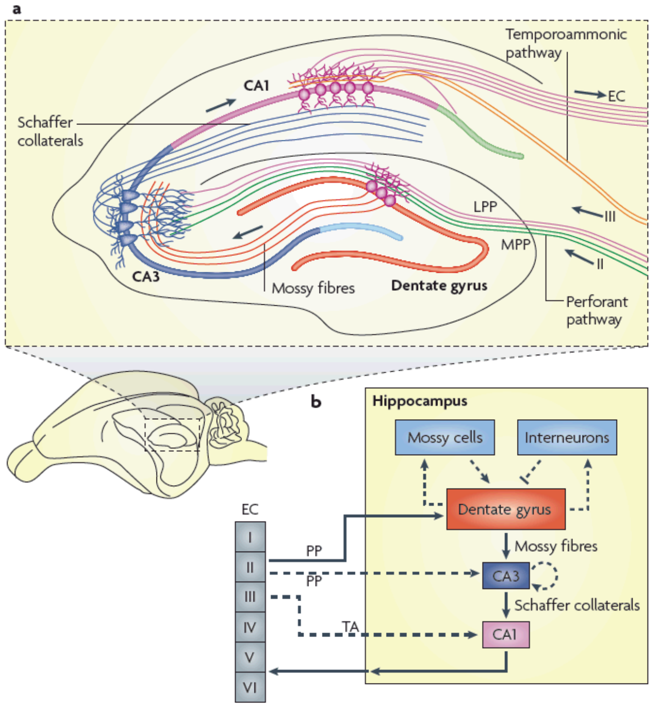
Dentate Gyrus

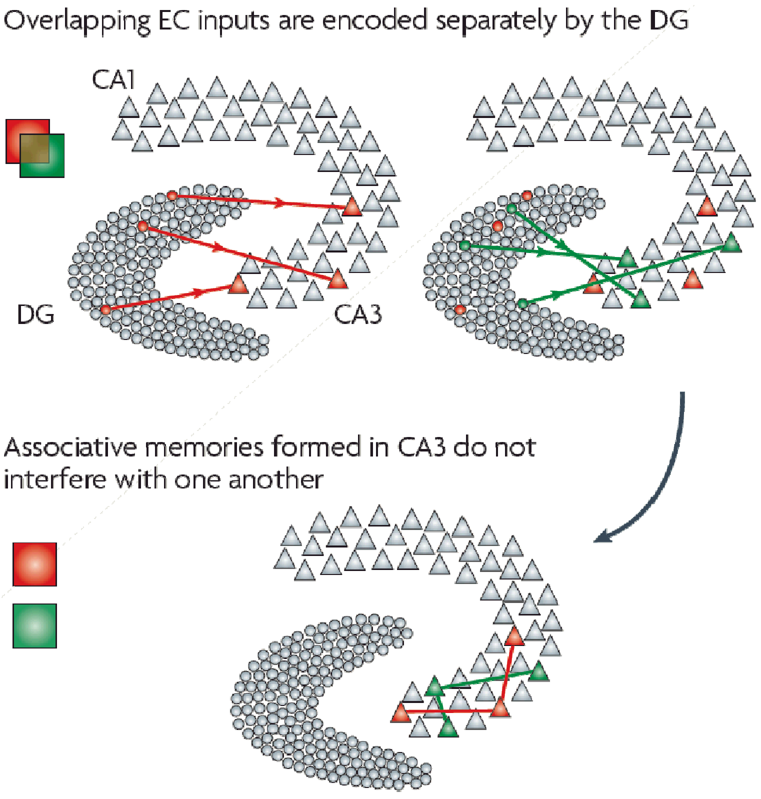
- First layer of classic trisynaptic loop
- Essentially feed-forward network (EC -> DG -> CA3) with some local feedback



Deng, Aimone, and Gage
Nature Reviews Neuroscience; 2010

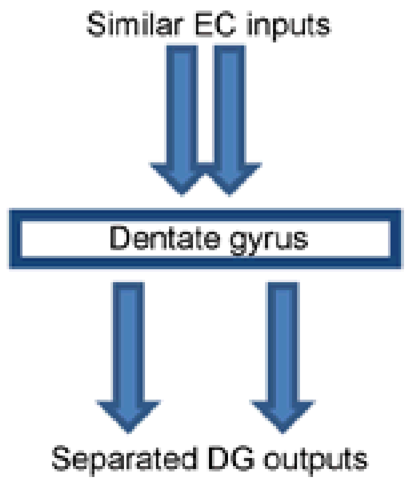
What does DG do?

- Pattern separation
  - Sparse, orthogonal representations of cortical inputs
  - Powerful projects drive encoding in CA3
- Conjunctive Encoding
  - Multimodal representation of diverse cortical inputs (spatial, objects, contextual, etc)



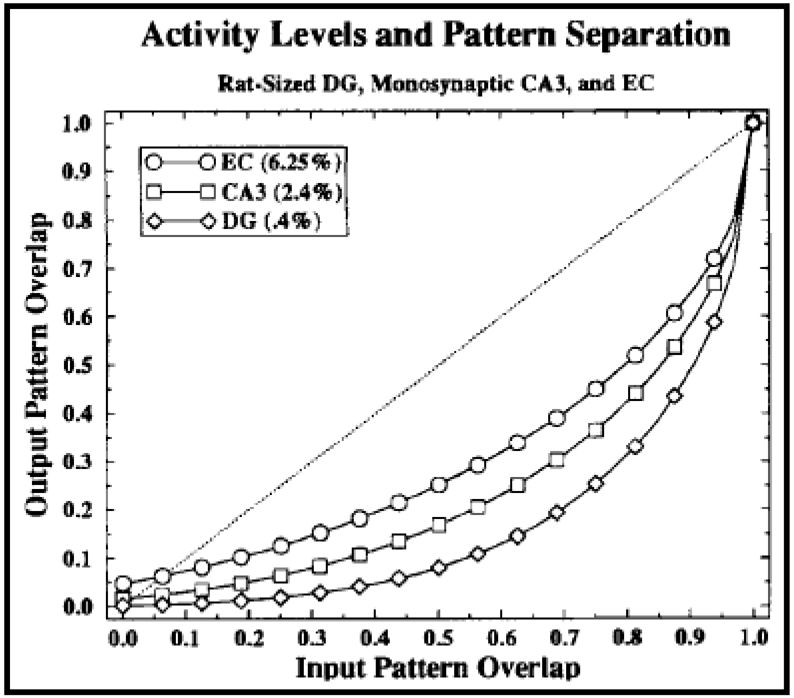
Deng, Aimone, and Gage
Nature Reviews Neuroscience; 2010

Readout of model: pattern separation in DG



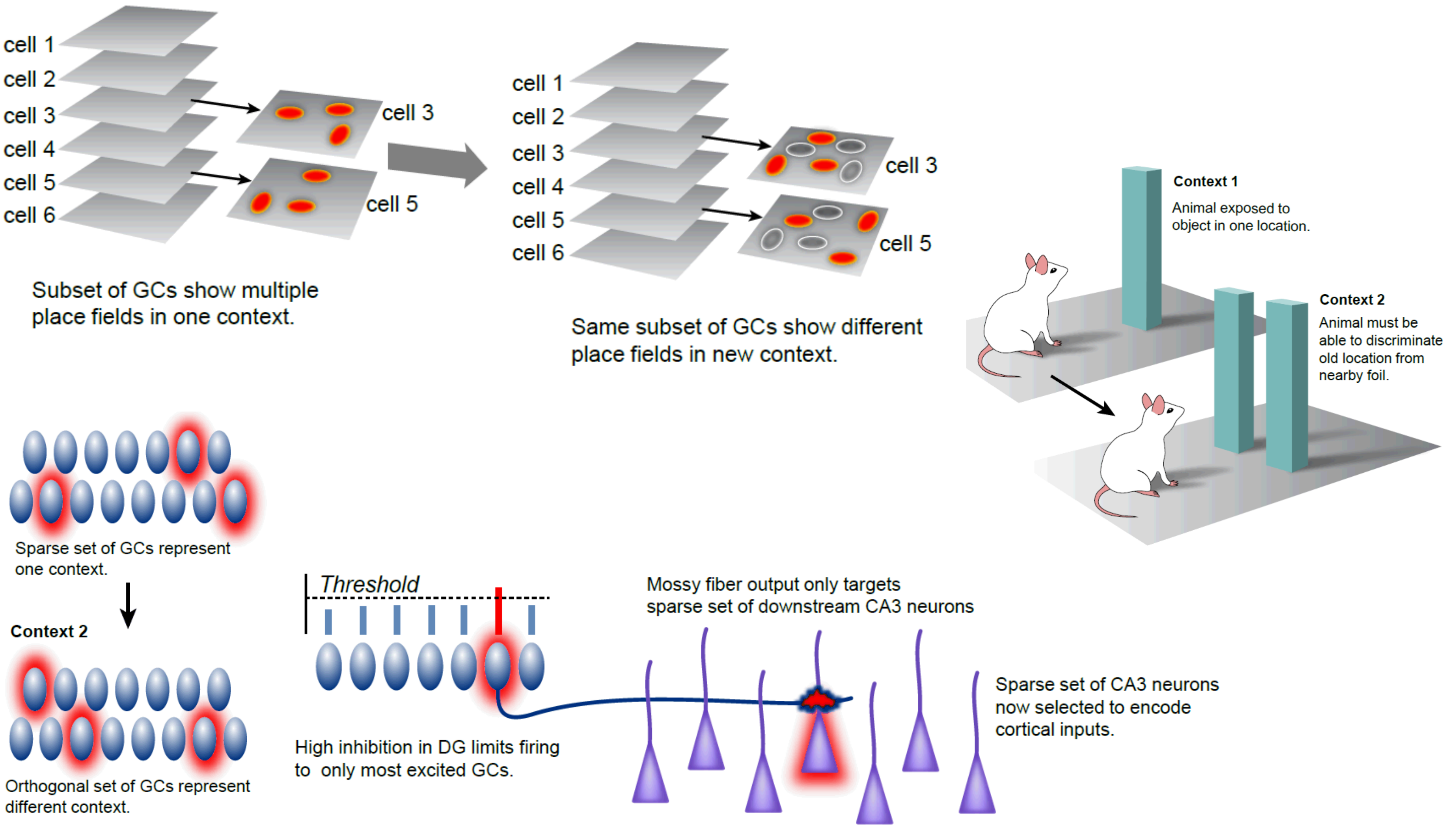
- Measure pattern separation in model by comparing similarity between inputs and outputs
  - Normalized dot product

$$NDP(\mathbf{x}_i, \mathbf{x}_j) = \frac{\mathbf{x}_i \bullet \mathbf{x}_j}{\|\mathbf{x}_i\| \times \|\mathbf{x}_j\|}$$



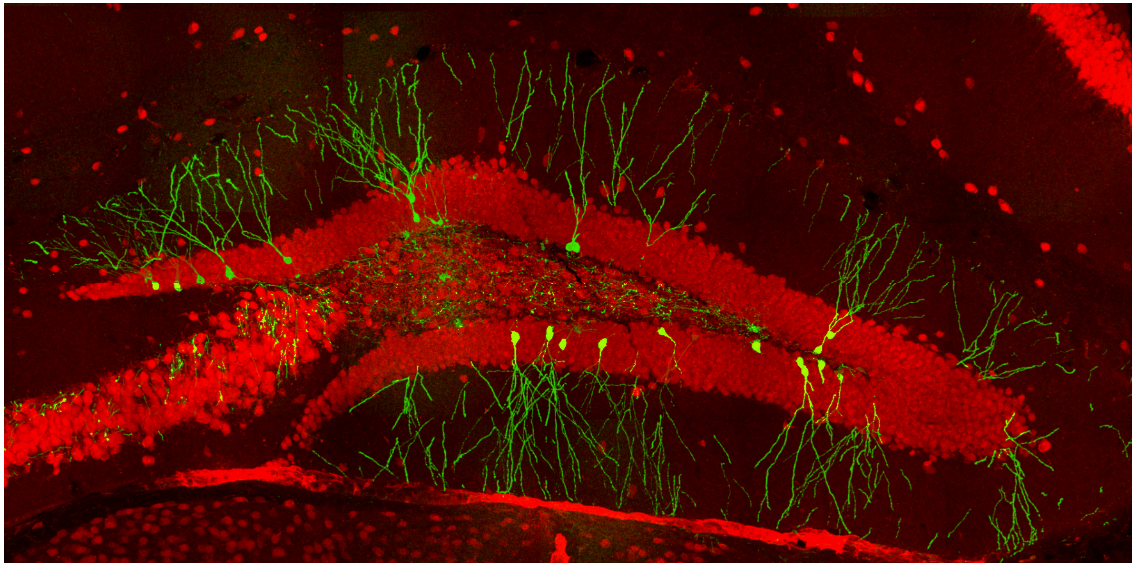
O'Reilly & McClelland, Hippocampus, 1994

What is pattern separation?



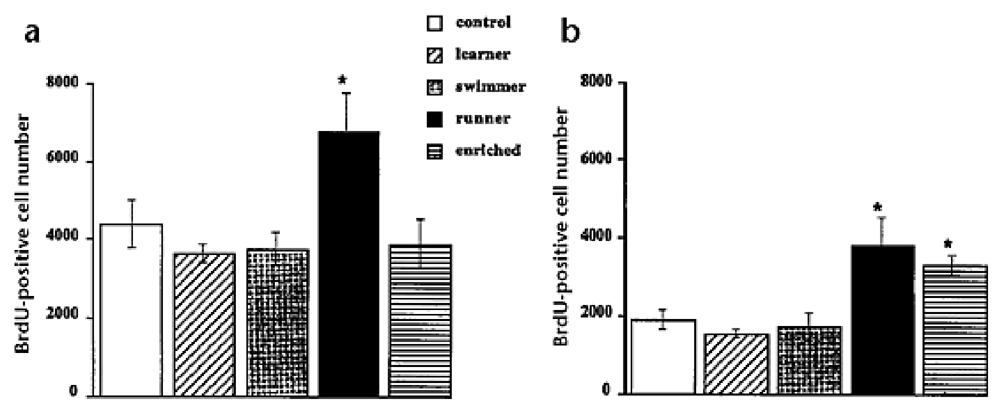
What is adult neurogenesis?

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



What is adult neurogenesis?

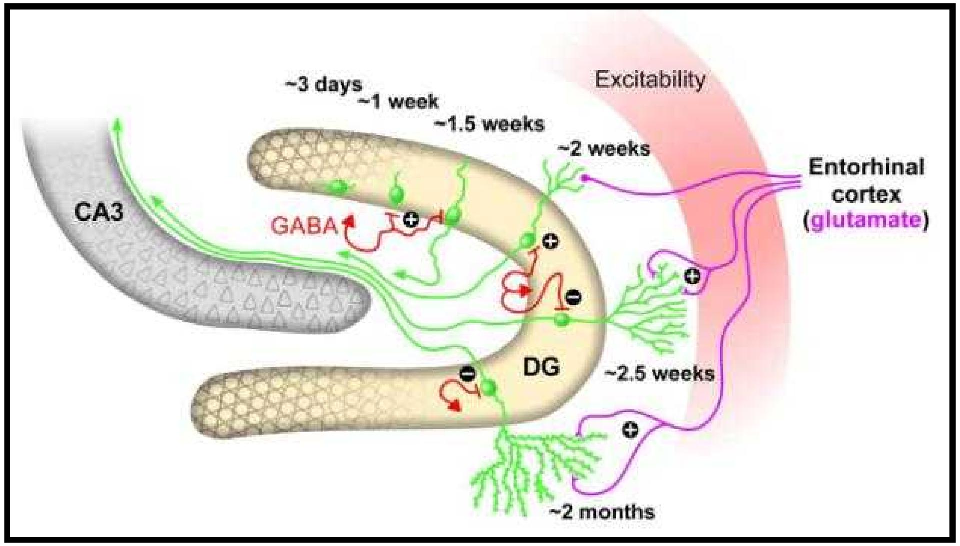
- Robust process
- Highly regulated
  - Both proliferation and survival controlled
  - Activity, enrichment, stress, diet, aging, disease…



van Praag et al., 1999

What is adult neurogenesis?

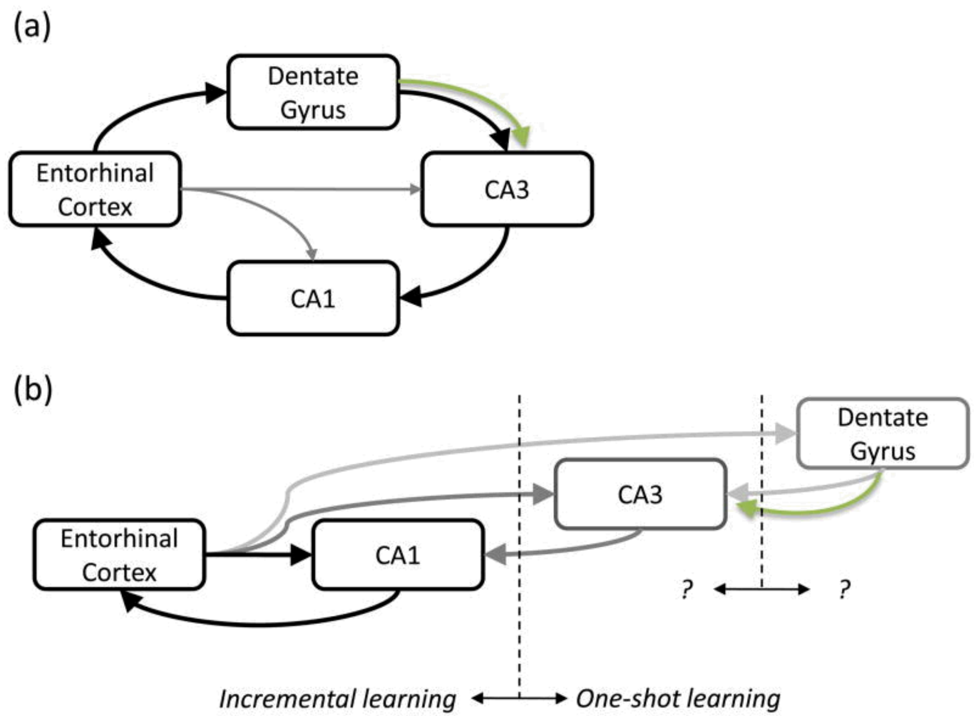
- Robust process
- Highly regulated
- Extended maturation
  - Several weeks to begin integrating into circuit
  - Still “immature” several months later



Aimone et al., Nature Neuroscience 2006

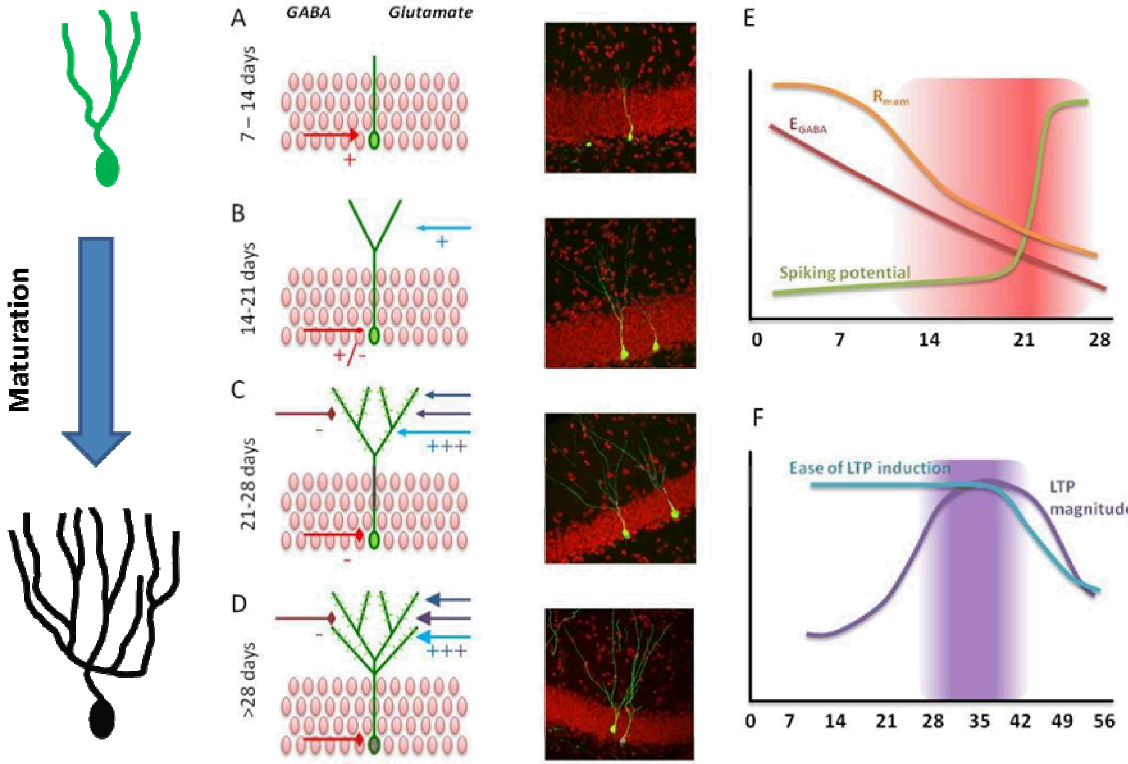
What is adult neurogenesis?

- 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

Maturation process of new neurons



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

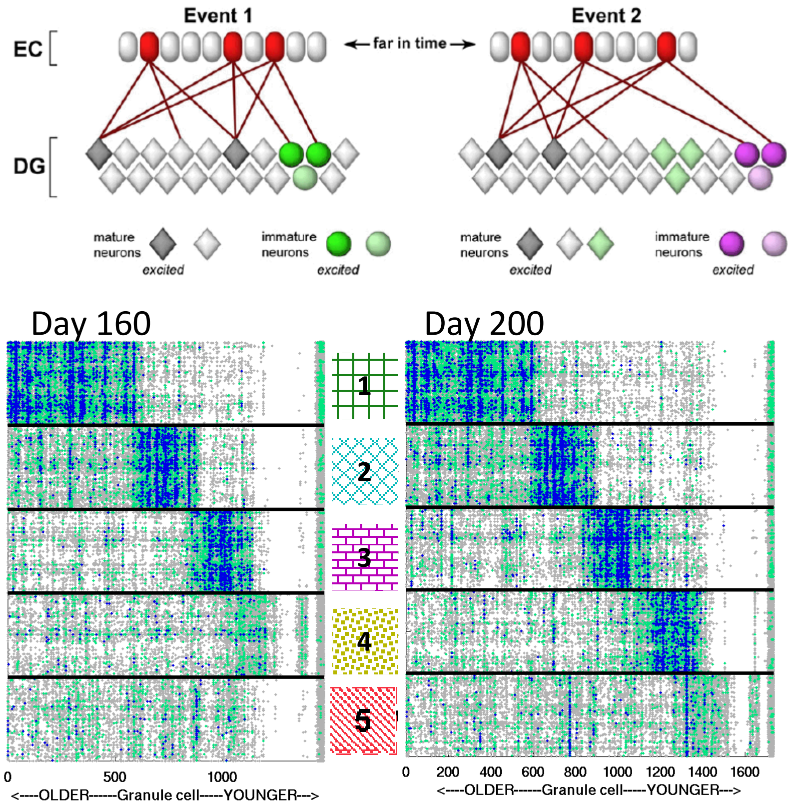
Adult Neurogenesis: Two Big Questions

- What does it do for cognition?

- Relevant in humans?

Summary of earlier modeling work

- Young neurons are transiently more active than mature neurons
  - Impair acute pattern separation?
- Different neurons active at different time yield temporal separation
- Maturation of young neurons allows "specialization" of DG to past events



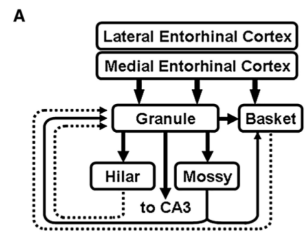
Aimone et al., Neuron 2009

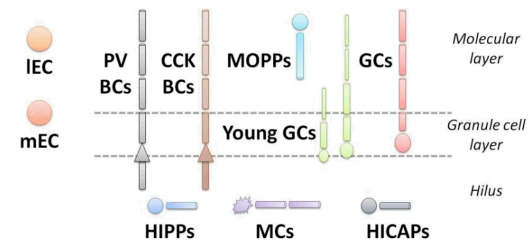
Spectrum of modeling: the added value of complexity

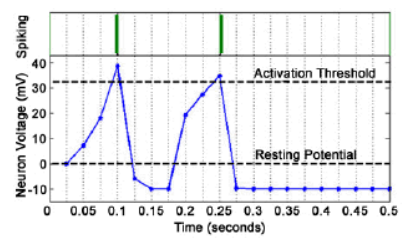
- Abstract
  - Assumptions in design and dynamics are very clear
  - Observed behaviors are easy to attribute to specific design principals
  - Relatively straightforward to do
- High Fidelity
  - Incorporates features whose importance is yet unclear
  - Highlights where biology data is strong and weak
  - Can reveal behaviors that were not a priori considered
  - Results can often be directly compared to biology

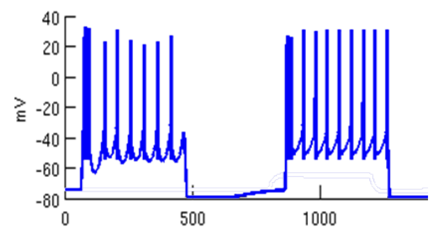
Limitations of past modeling work

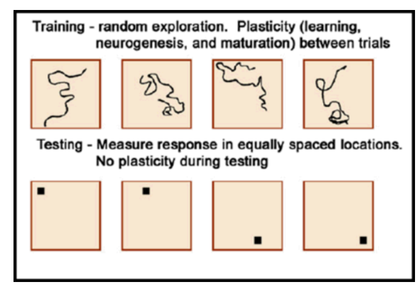
- Between abstract and high fidelity
  - Time not particularly well represented
  - Details of DG architecture lost (e.g., feed-forward inhibition, modulatory inputs)
  - Experiment doesn't map to behavior

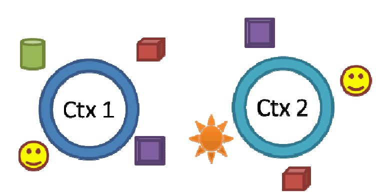






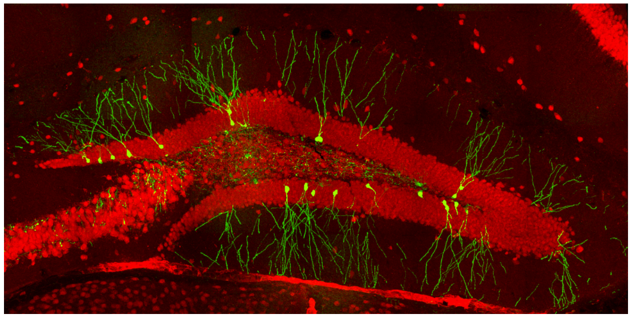




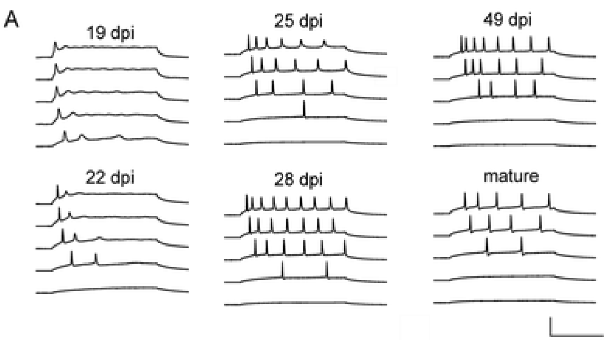


Aimone et al., Neuron 2009

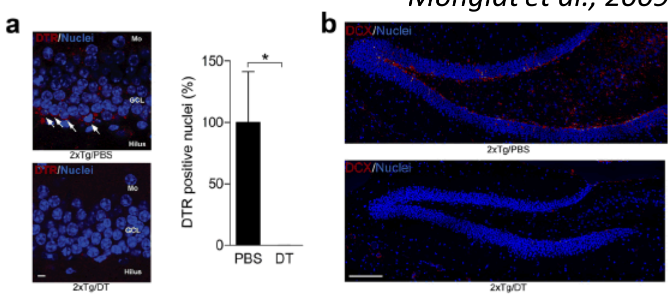
Modeling considerations



courtesy Chunmei Zhao



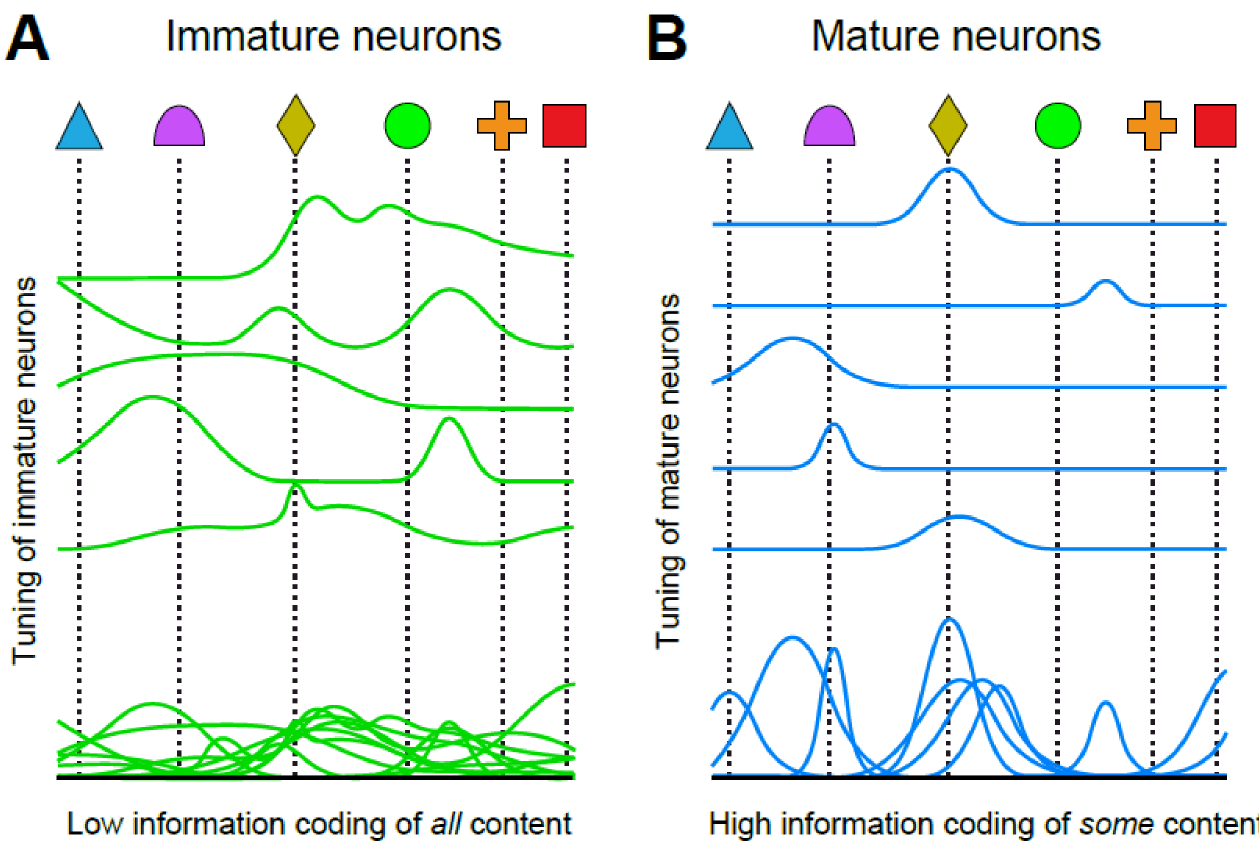
Mongiat et al., 2009



Arruda-Carvalho et al., 2011

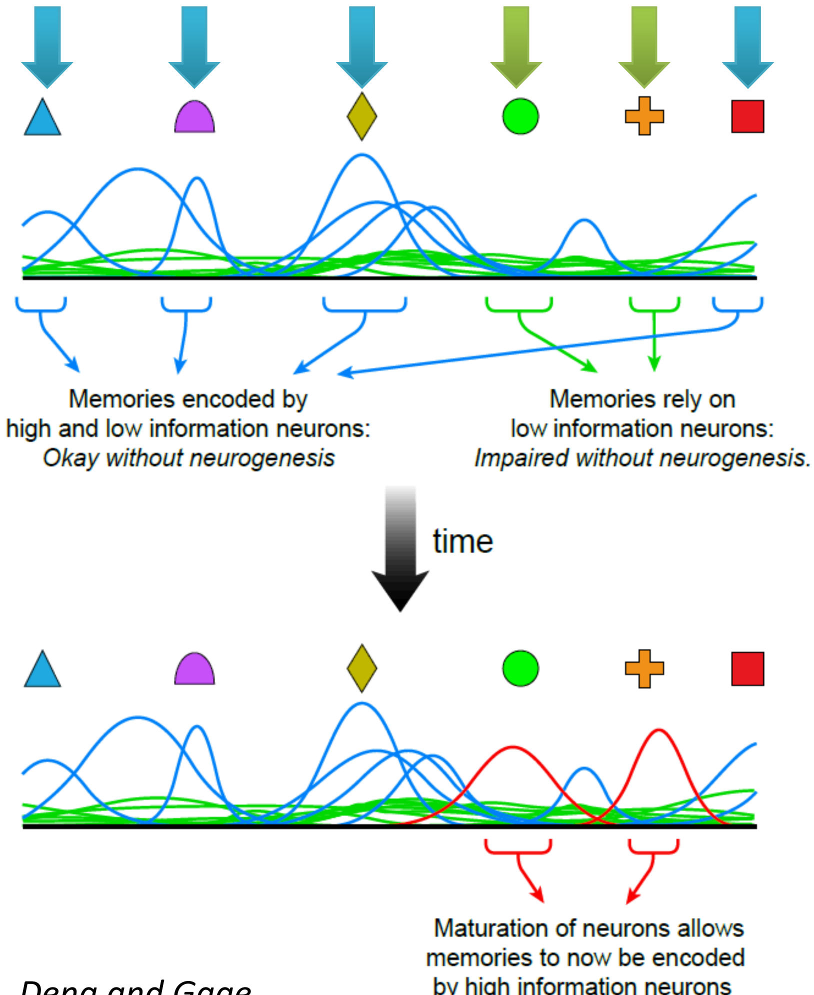
- Neuroanatomy
  - Circuit (principal neurons, interneurons, and how they are connected)
  - Maturation of new neurons
- Dynamics
  - Every neuron has unique dynamics
  - Neurogenesis results in many different forms of GC dynamics
- Behavior
  - *In vivo* and immediate early gene studies of neuron behavior
  - Behavior studies in lesion or knockdown animals

Immature and mature neurons encode information differently



Aimone, Deng and Gage
Neuron; 2011

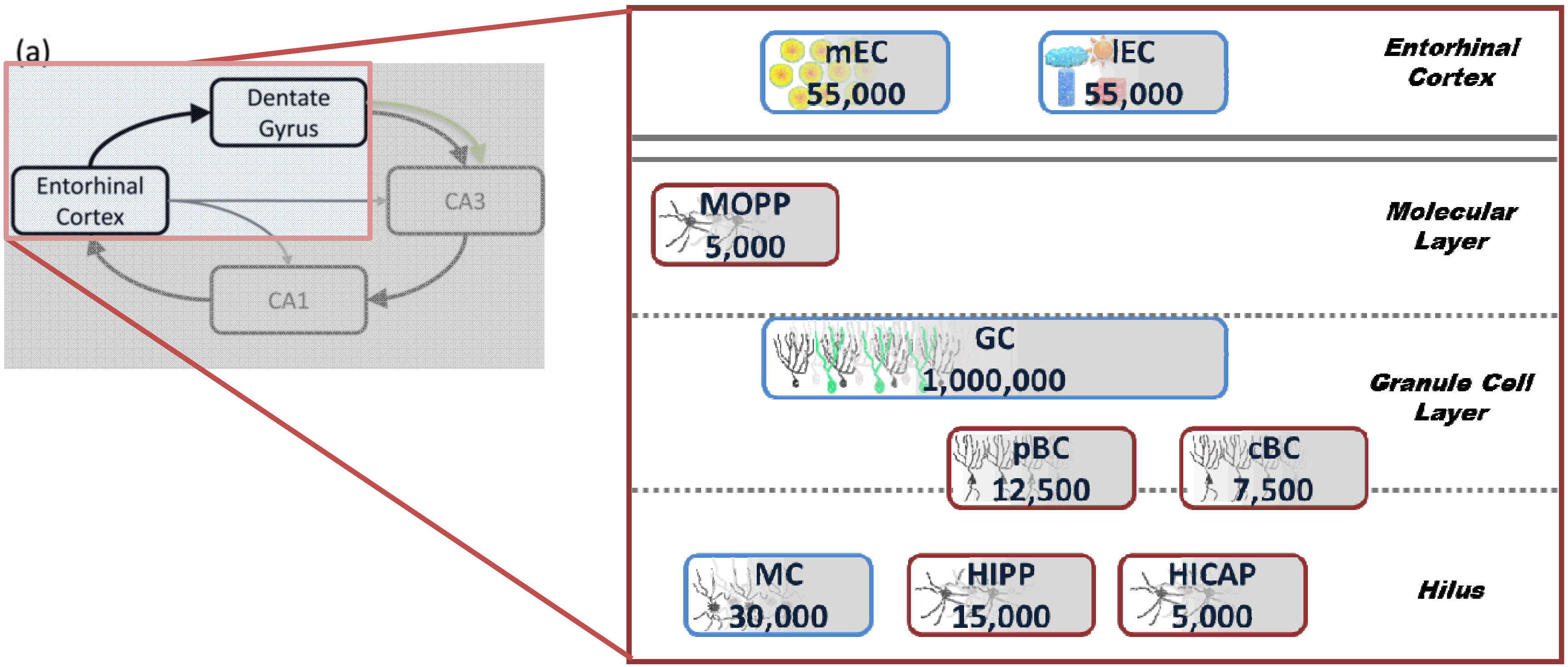
Mixed coding scheme in DG is potentially very powerful



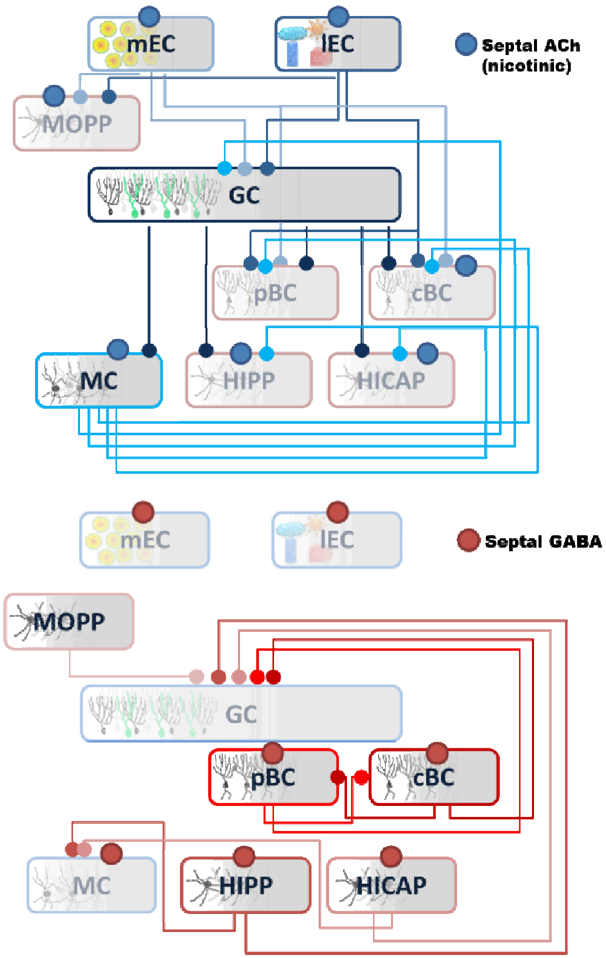
Aimone, Deng and Gage
Neuron; 2011

- Dentate Gyrus performs sparse coding for episodic memories
- Mature neurons are tightly tuned to specific features
  - *Not all events will activate mature neurons*
- Immature neurons are broadly tuned
  - *All events will activate some immature neurons*
- Neurons mature to be specialized to those events later
  - *Coding range of network gets more sophisticated over time*

Realistic scale model

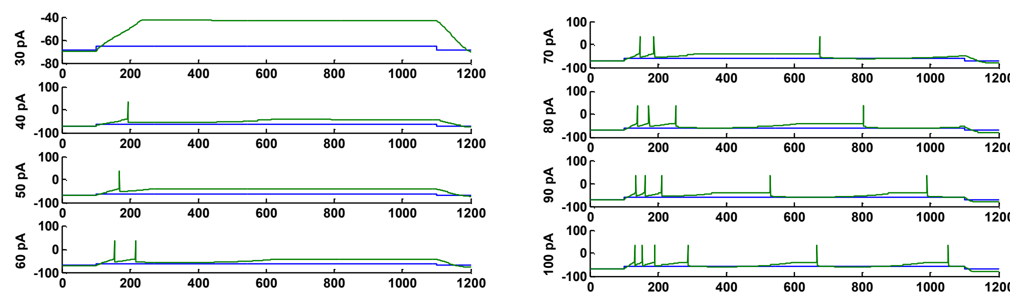


Realistic connectivity and dynamics

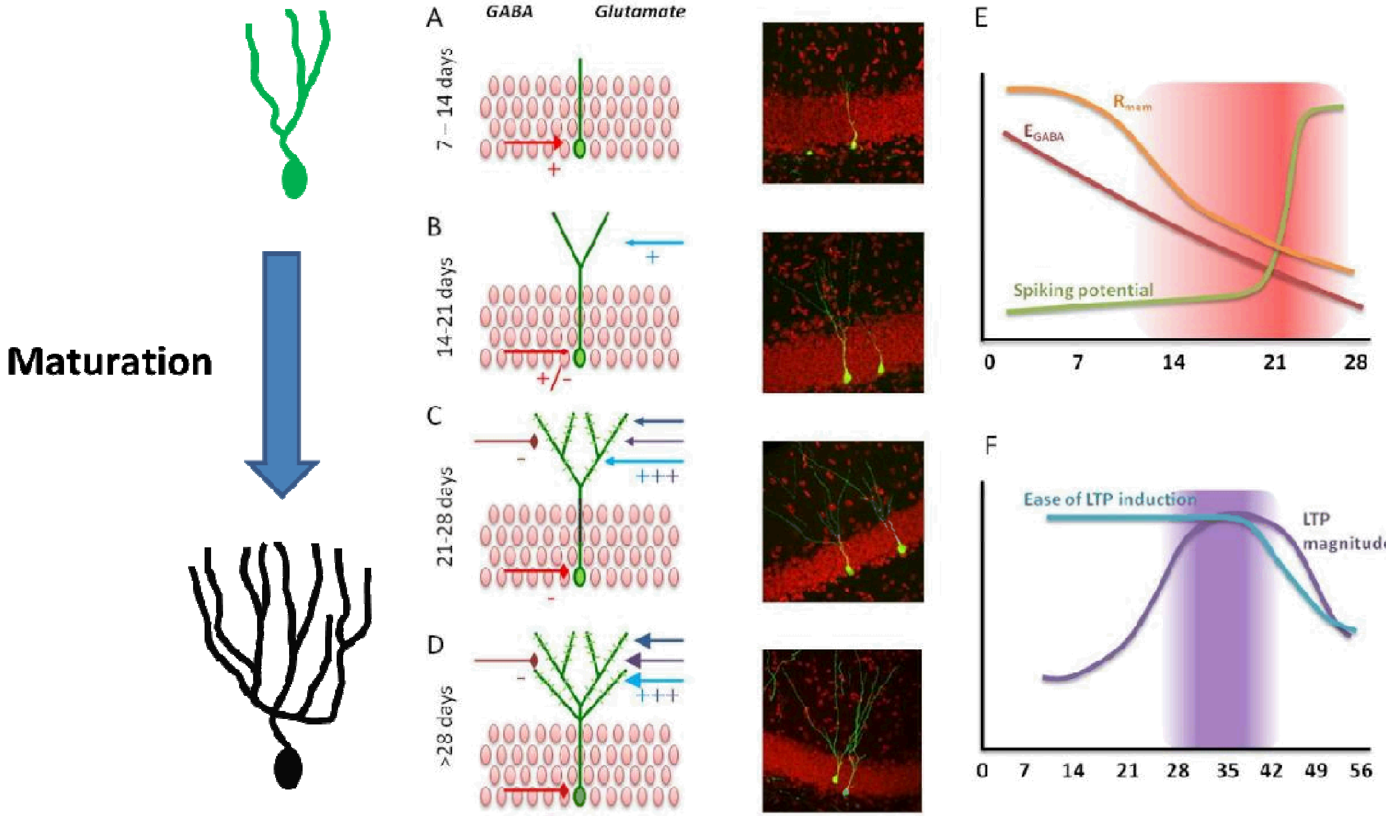


Physiology data

Modeled neuronal dynamics

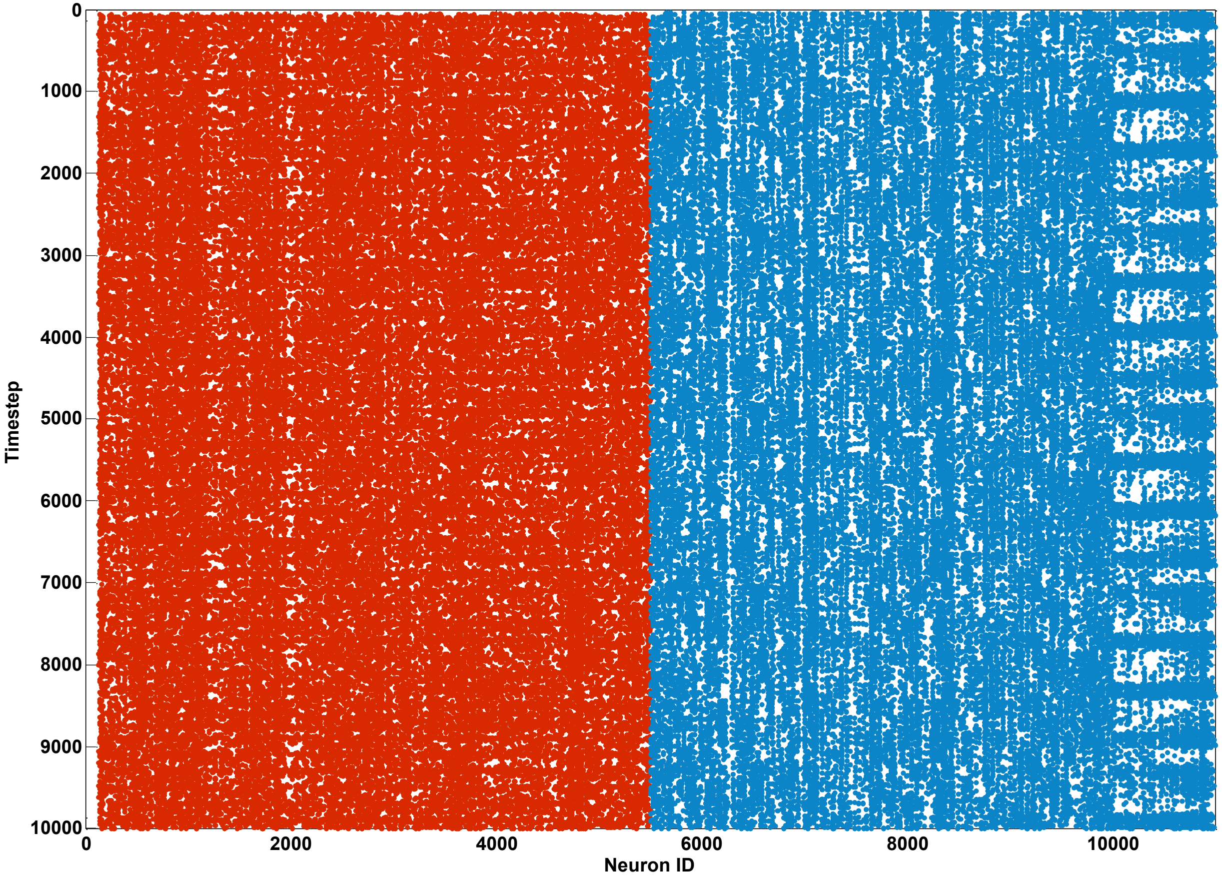


Neurogenesis Process

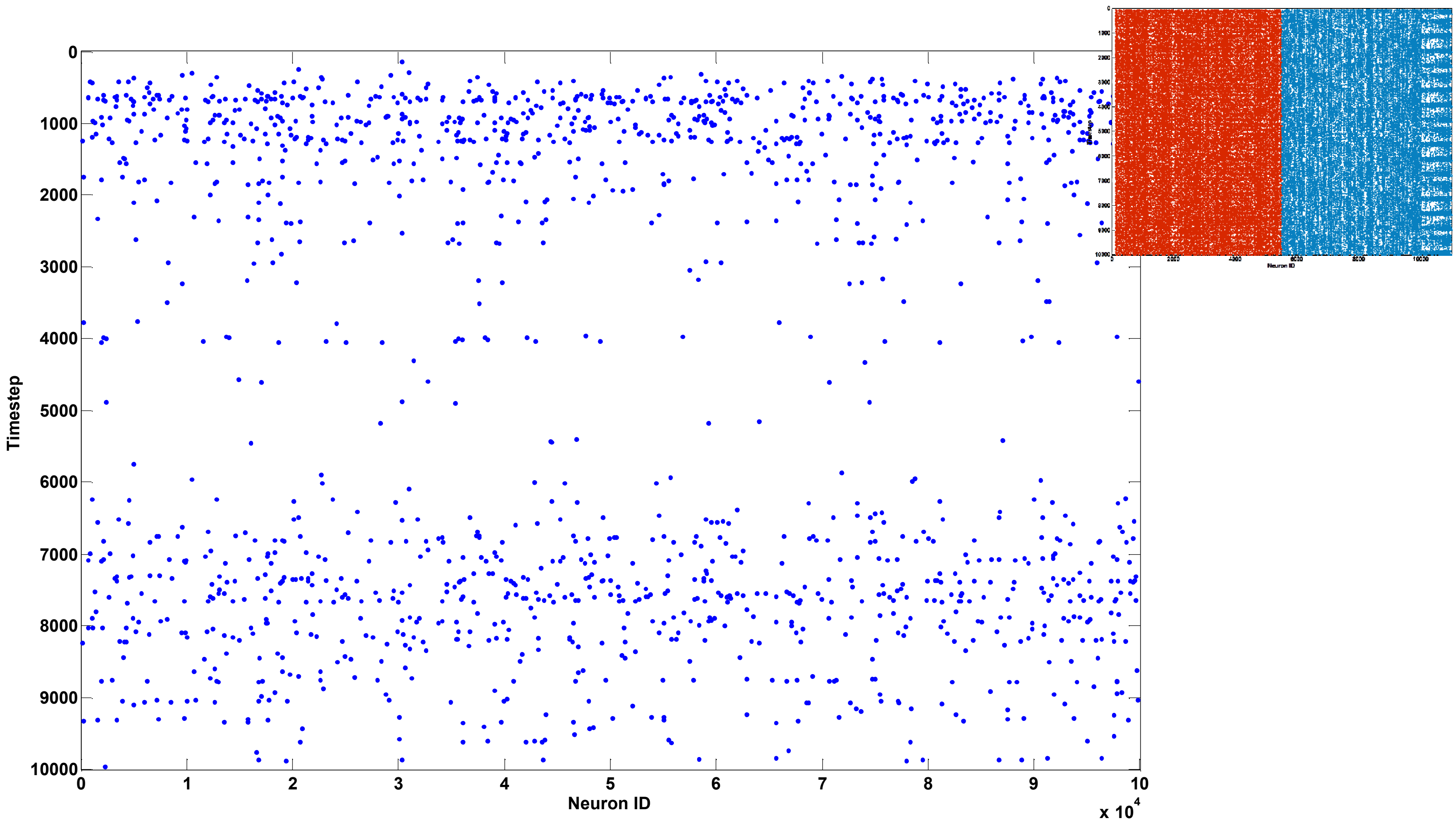


Aimone, Deng, and Gage
Trends in Cog. Sci. 2010

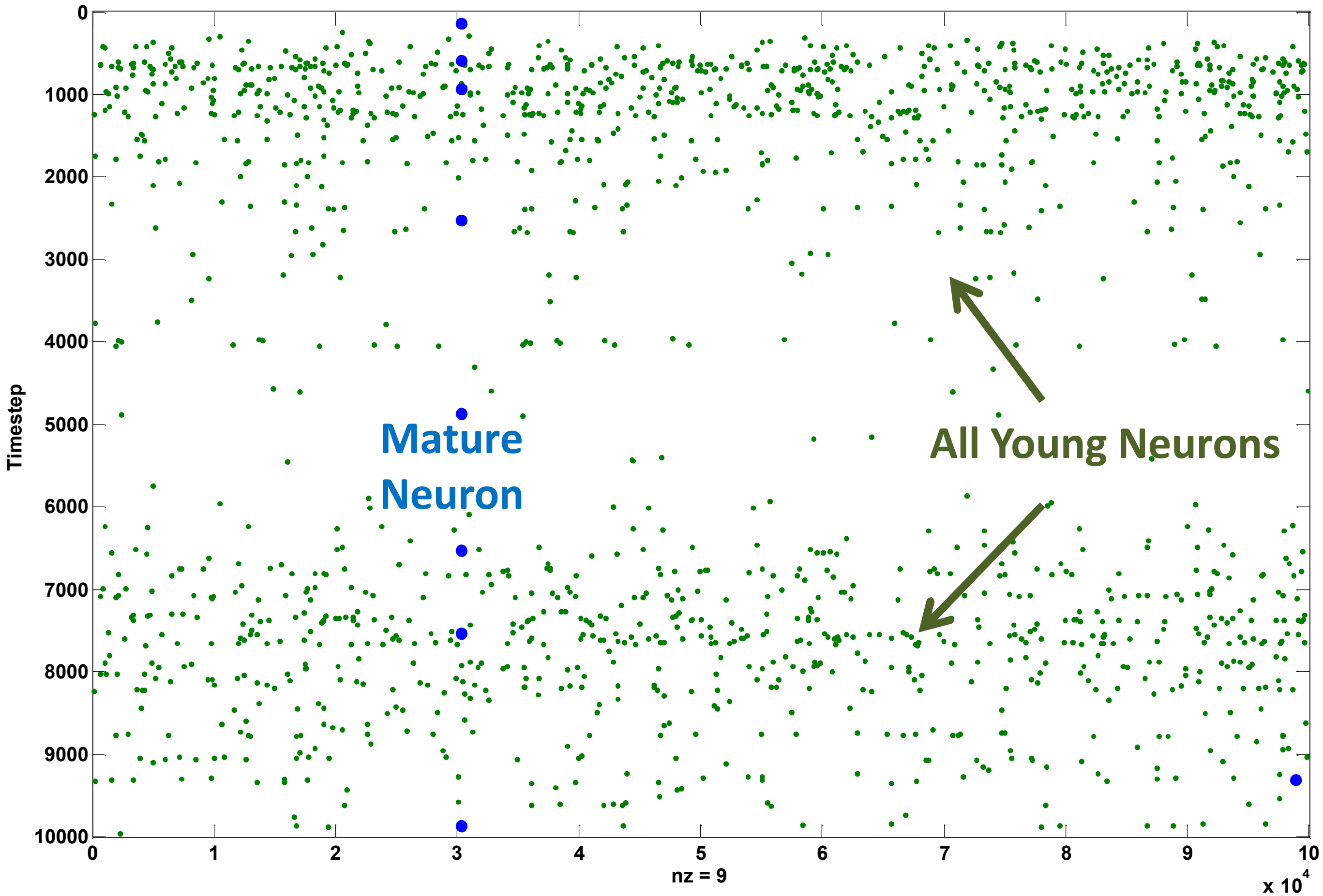
Activity of network – EC Inputs



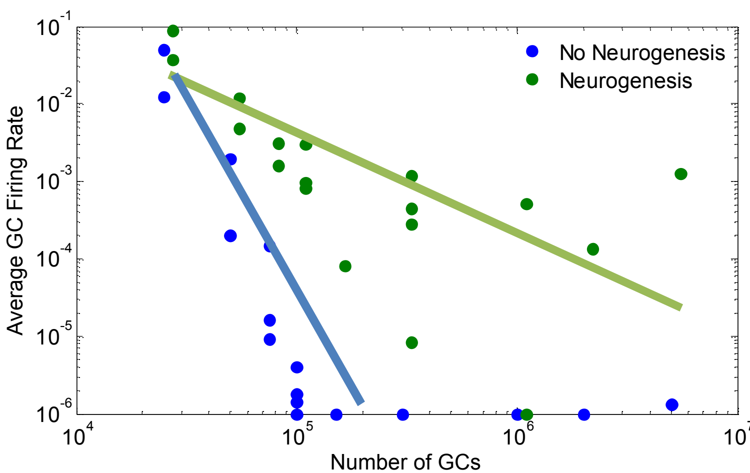
Activity of network – GC Outputs



Young GCs dominate

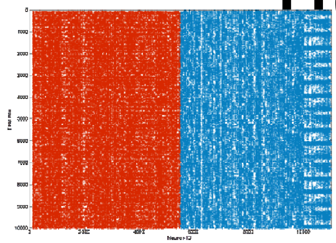


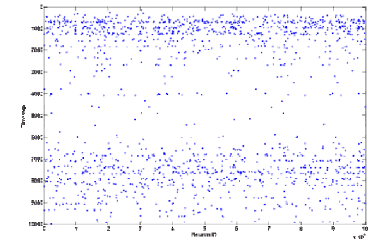
Lack of neurogenesis in large networks correlates with much lower activity

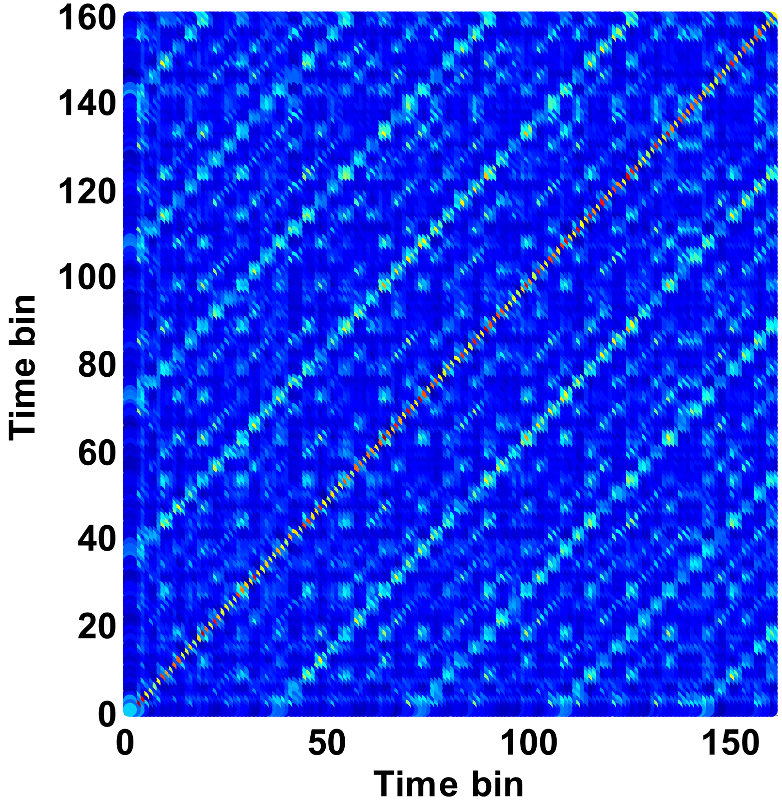


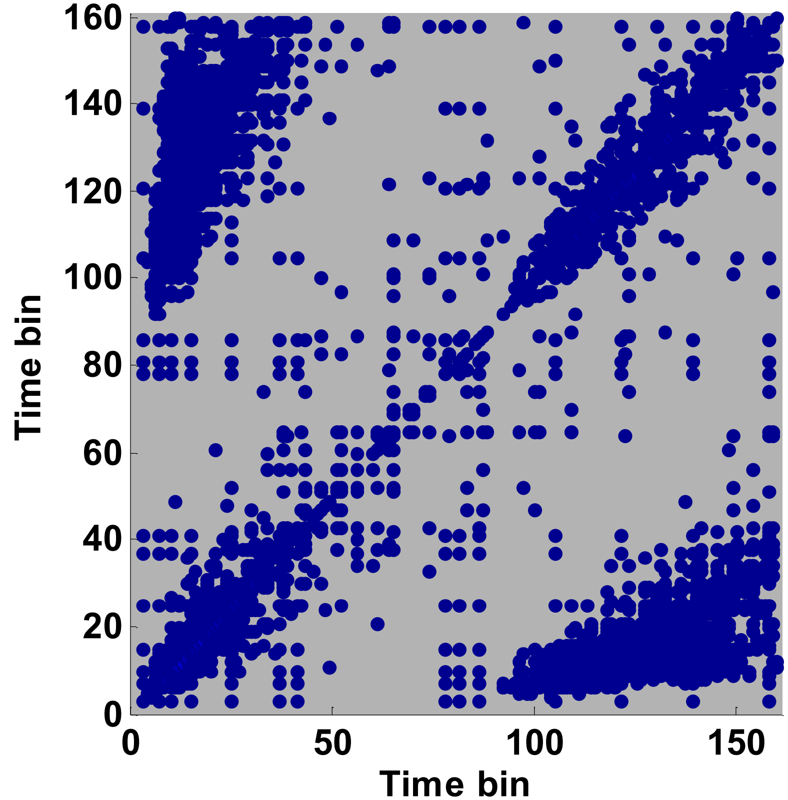
- Neurogenesis networks show activity to novel information at much higher scales
- As we approach human scales, mature neurons appear essentially silent in response to novel information
- Signal (immature) to noise (mature) is amplified in larger networks

Information processing in large networks

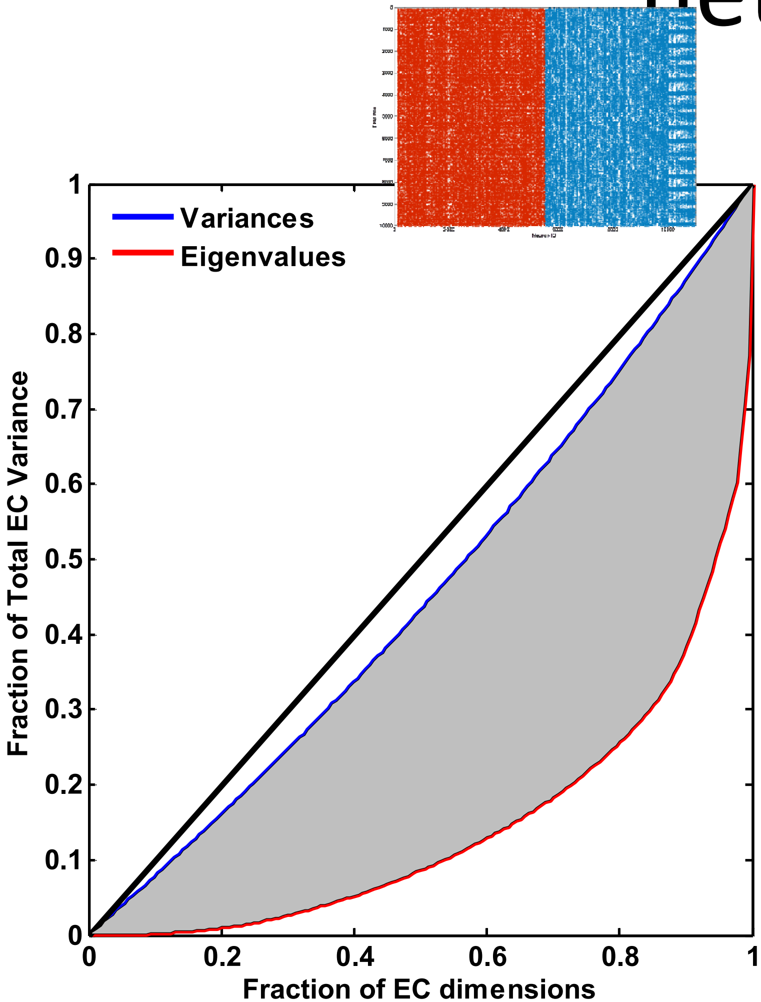


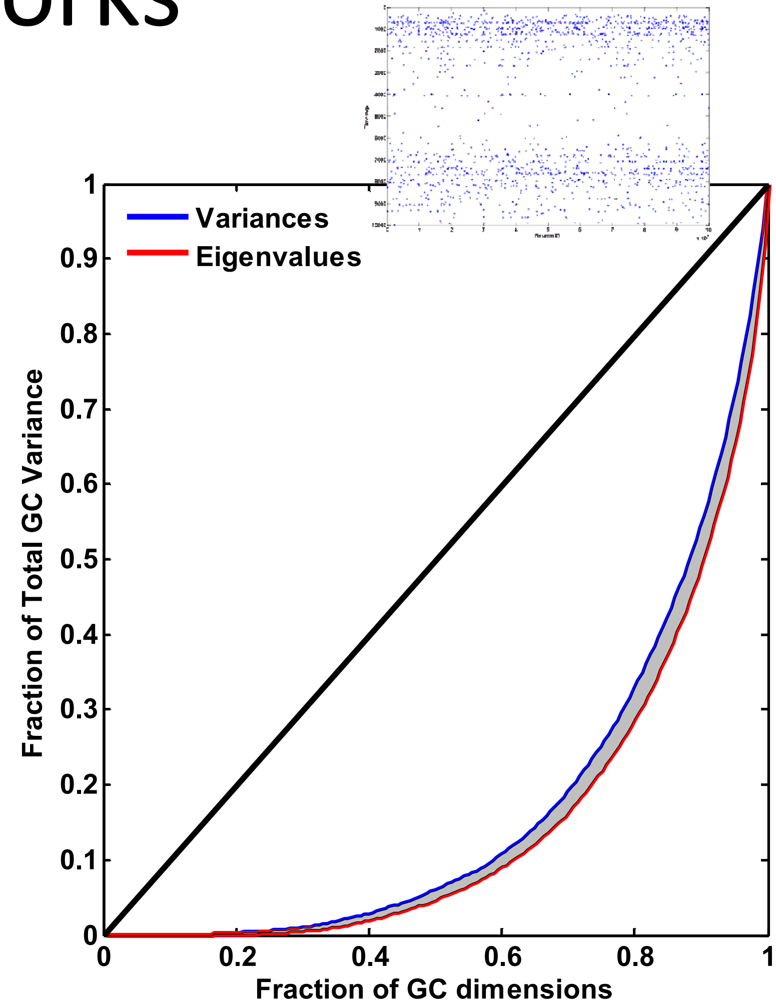




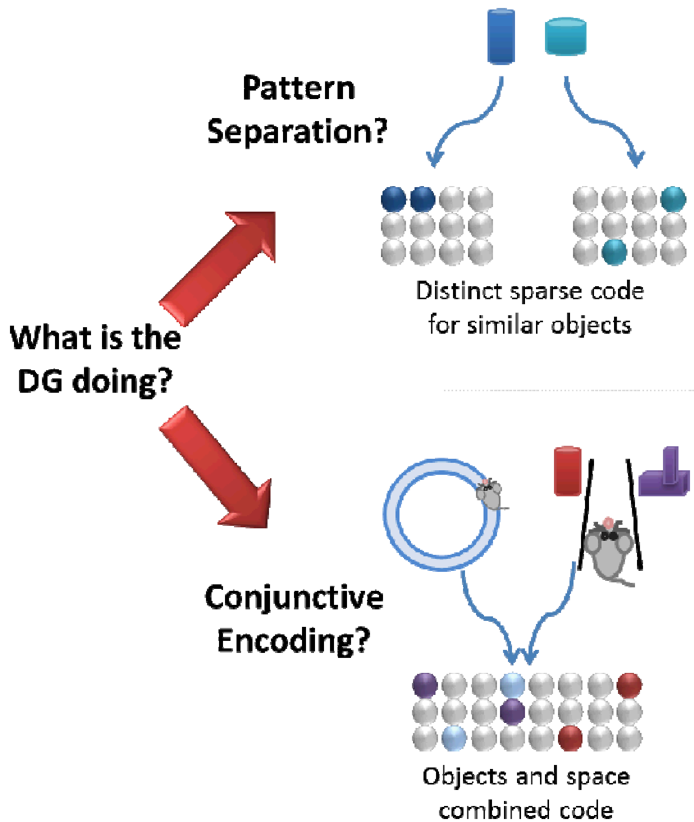


Information processing in large networks





Metrics for understanding NG model



- Pairwise correlation / dot product

$$Sim_{t1,t2} = \frac{\|f_{GC,t1} \cdot f_{GC,t2}\|}{\|f_{GC,t1}\|\|f_{GC,t2}\|}$$

- Average covariance

$$\sigma_{t1,t2} = \sum_{GC} (f_{GC,t1} - f_{t1}) \cdot (f_{GC,t2} - f_{t2})$$

How to combine over observations?

- **Linear compressability**

$$\kappa_{GC} = \sum_{i=1..d}(\sigma_i - \lambda_i) \Big/ \sum_{i=1..d} \sigma_i$$

- Average firing rate

$$f_{GC} = 1/N_{GC} \sum_{GC} N_{spikes}/T$$

- Total variance

$$\sigma_{GC} = \sum_{T} \sigma_{GC,T}$$

- Information Content

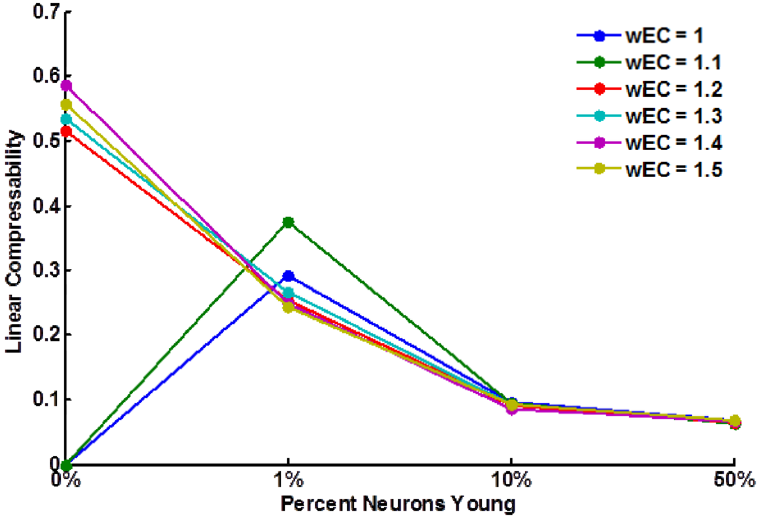
$$I = \sum_{ctx} p_{ctx} \, f/f \, \log_2 f/f$$

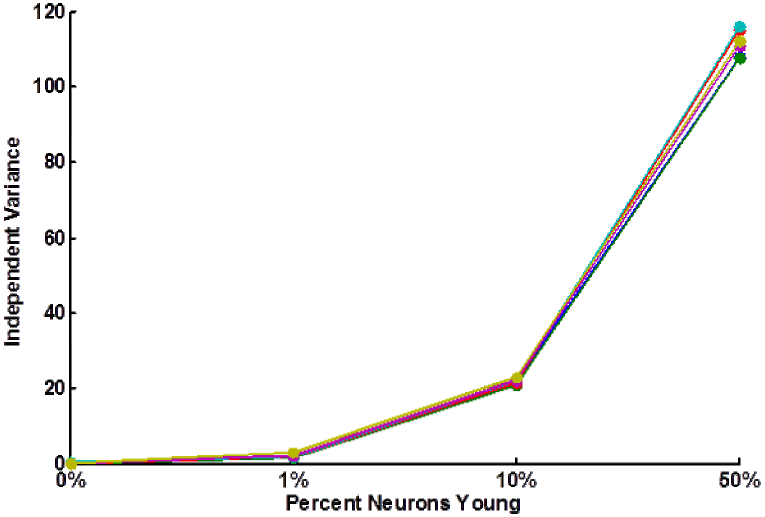
How to combine over neurons?

- **Independent variance**

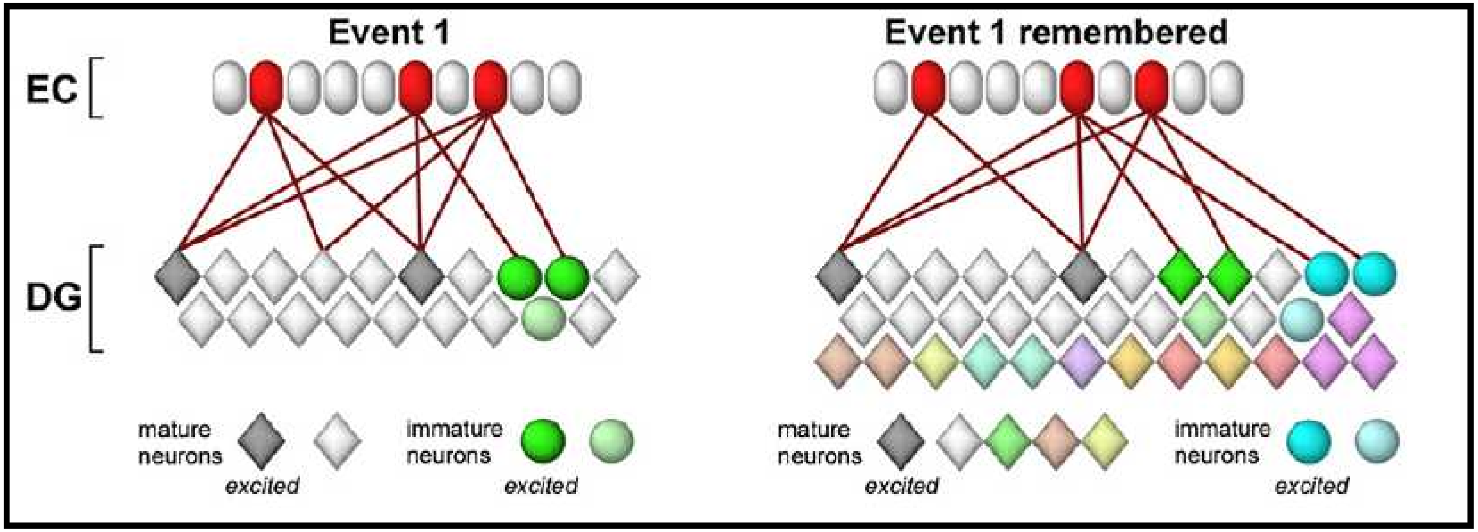
$$\varphi_{GC} = \sigma_{GC} \times \kappa_{\lambda}$$

Neurogenesis decreases compressibility and increases total representation





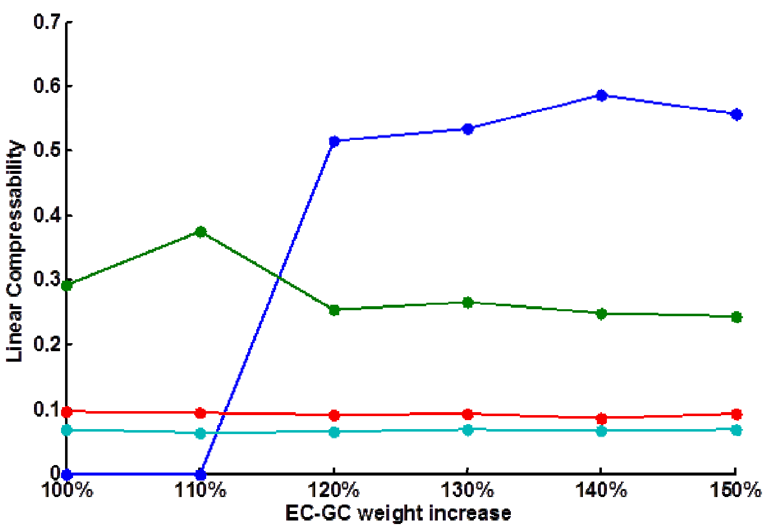
Environmental commitment of adult-born neurons

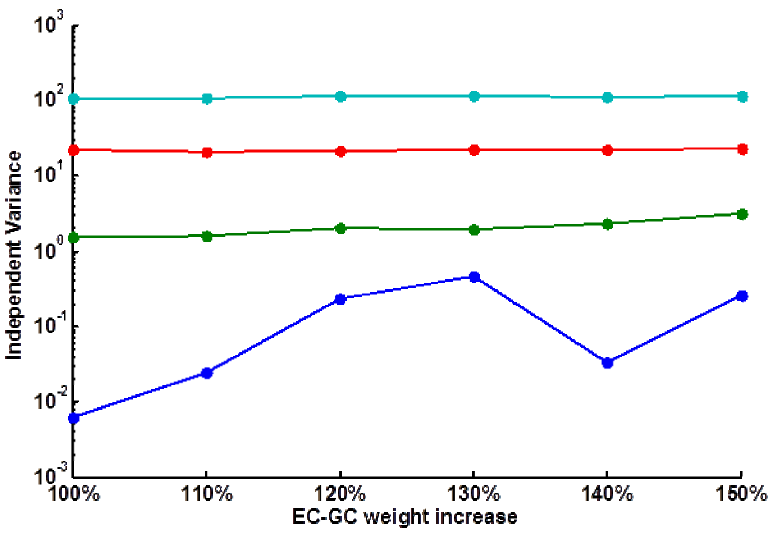


Aimone et al., Neuron 2009

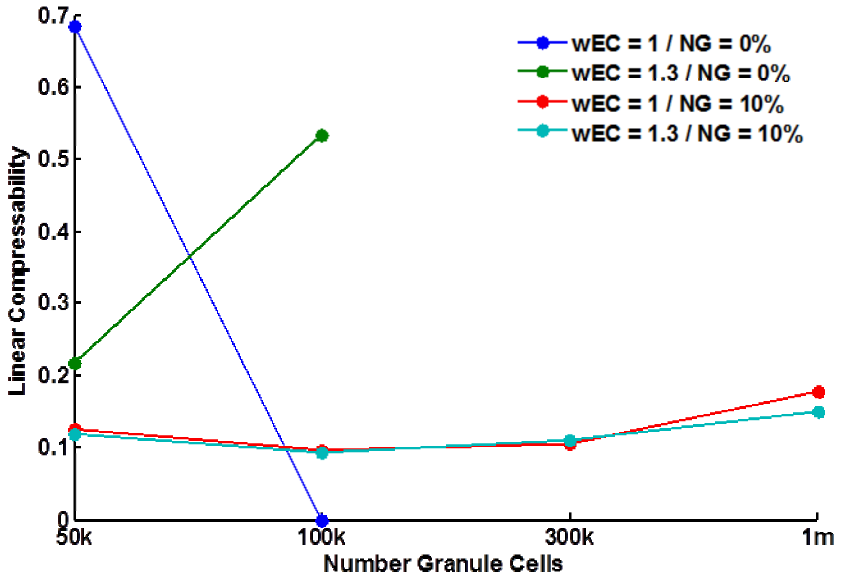
Hypothesis: The specialization of young neurons to the environments present during maturation allows improved encoding of new memories that relate to previously experienced contexts.

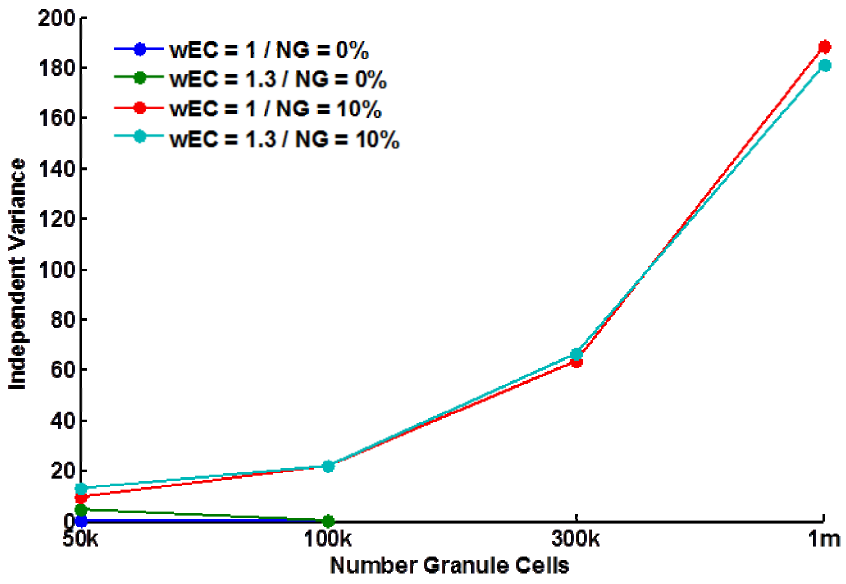
Increasing EC-GC weights impairs separation without improving coding



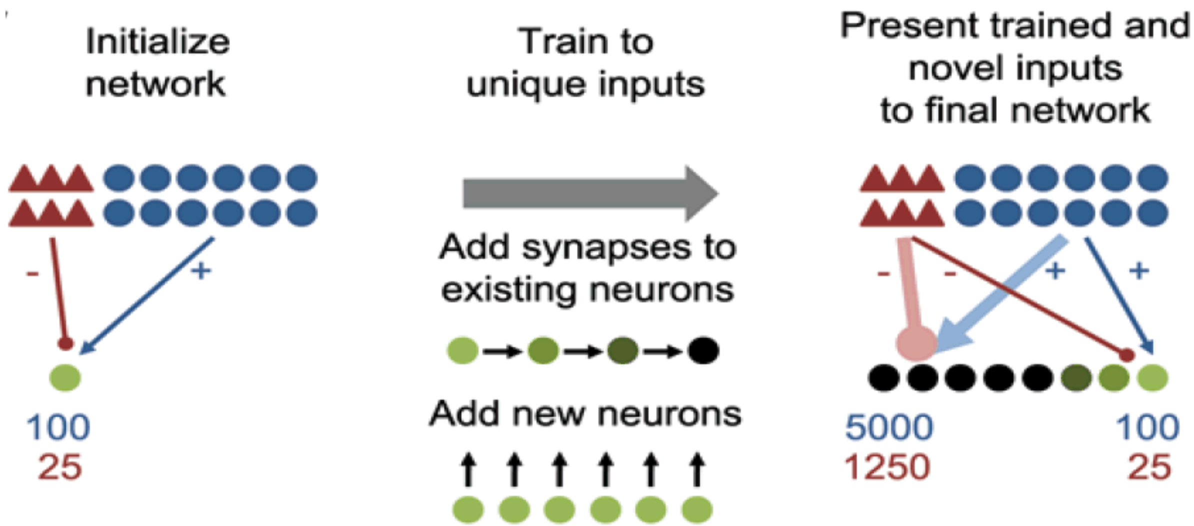


Increased size networks need neurogenesis for balancing separability and representations





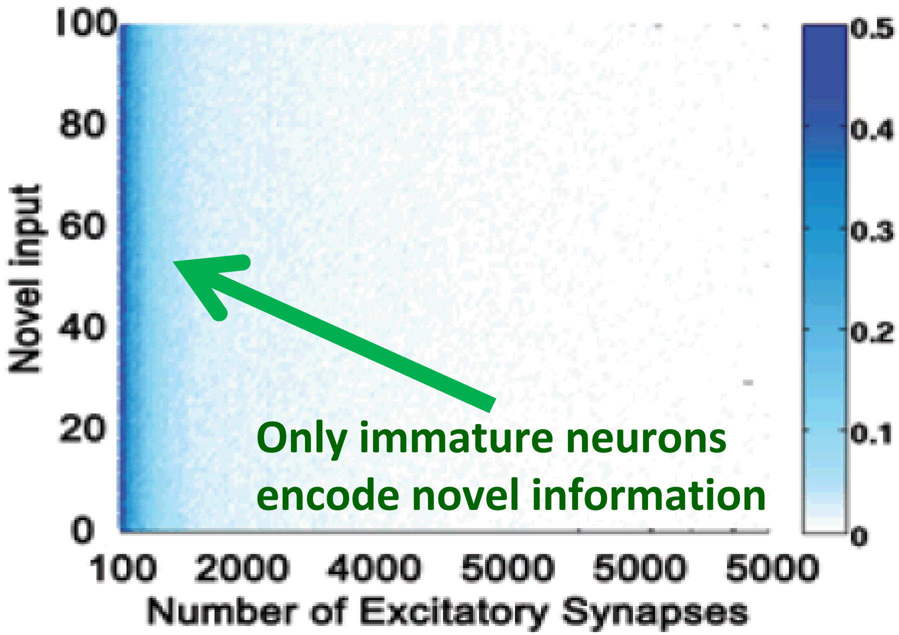
Abstract model: scaling neuron sizes yields neurogenesis effect



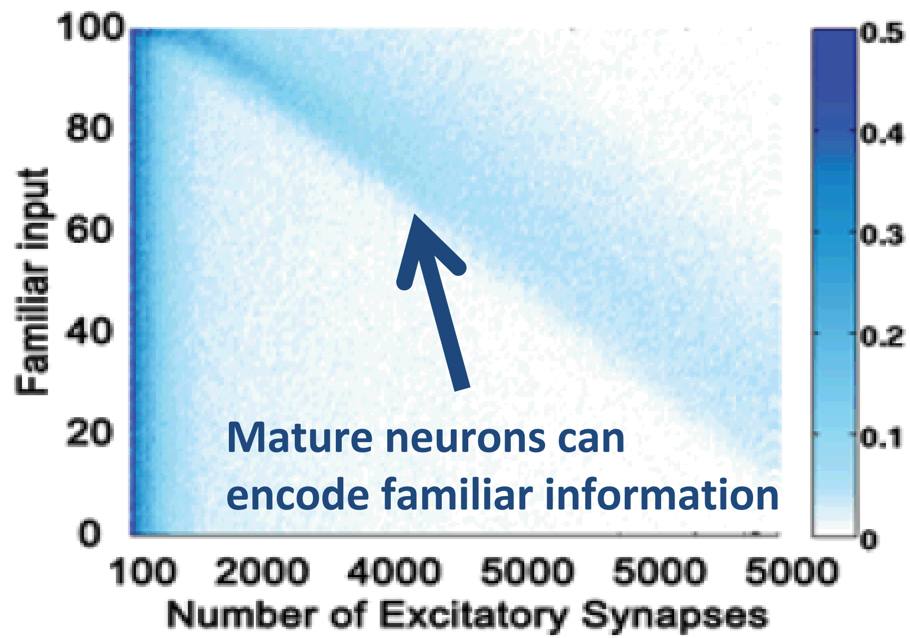
Li, Aimone et al., PNAS 2012

Neurons maturing to large number of synapses contain high information about maturation cues

Novel Inputs

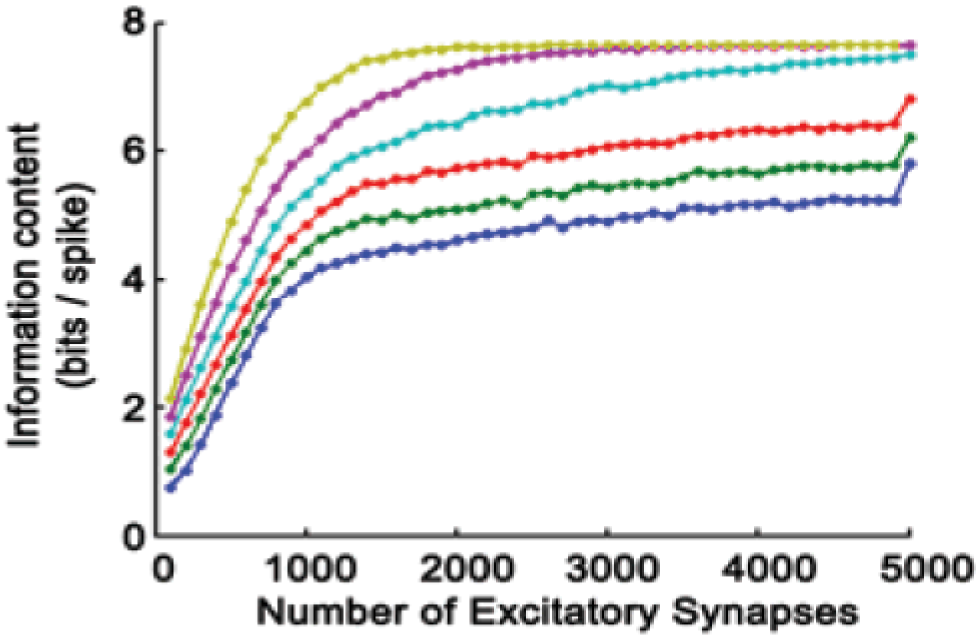


Trained Inputs



Li, Aimone et al., PNAS 2012

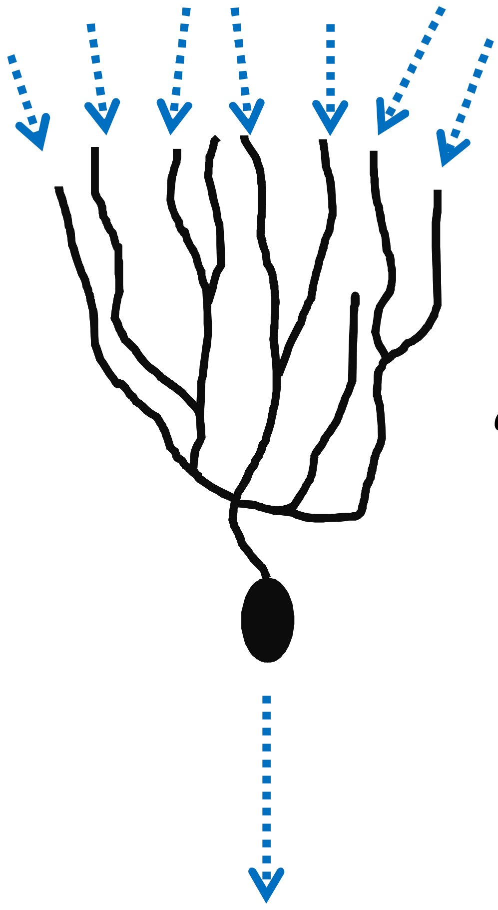
High synapse neurons have higher information content

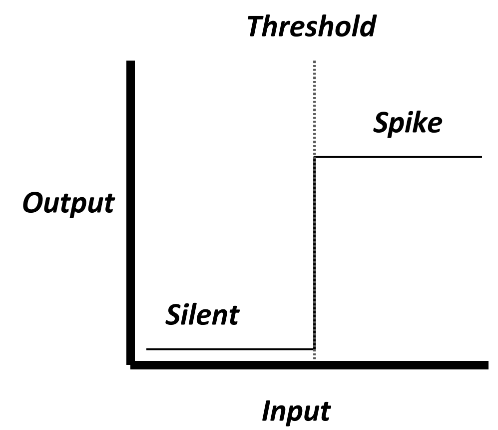


Li, Aimone et al., PNAS 2012

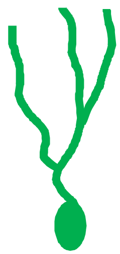
Simple example of scaling dimensionality

- Simple binary threshold neuron
- Input are many different synapses
- Cell “fires” if inputs surpass a threshold
  - Threshold is typically many inputs active at the same time

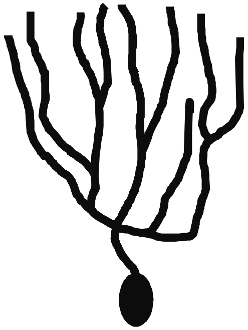




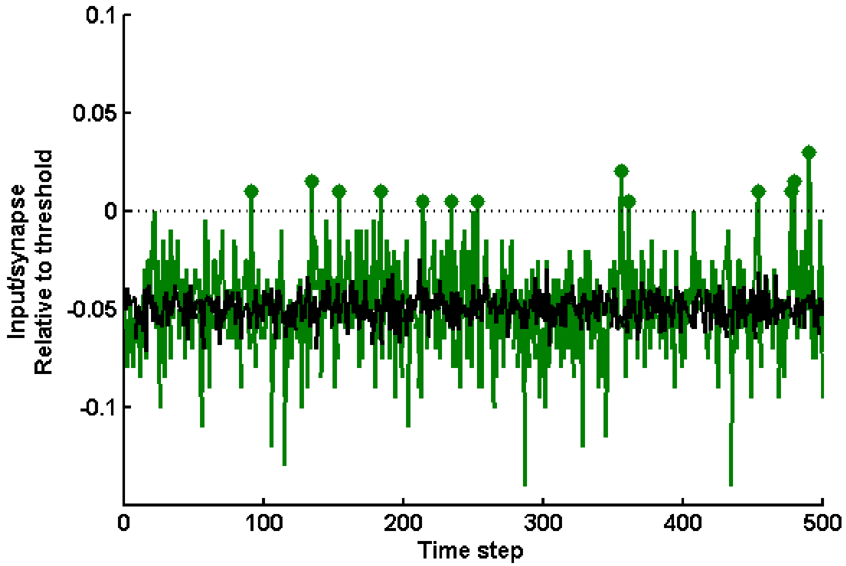
Noise affects lower dimensional neurons



200 synapses
25% (50) active
required to fire
20% (40) active on
average

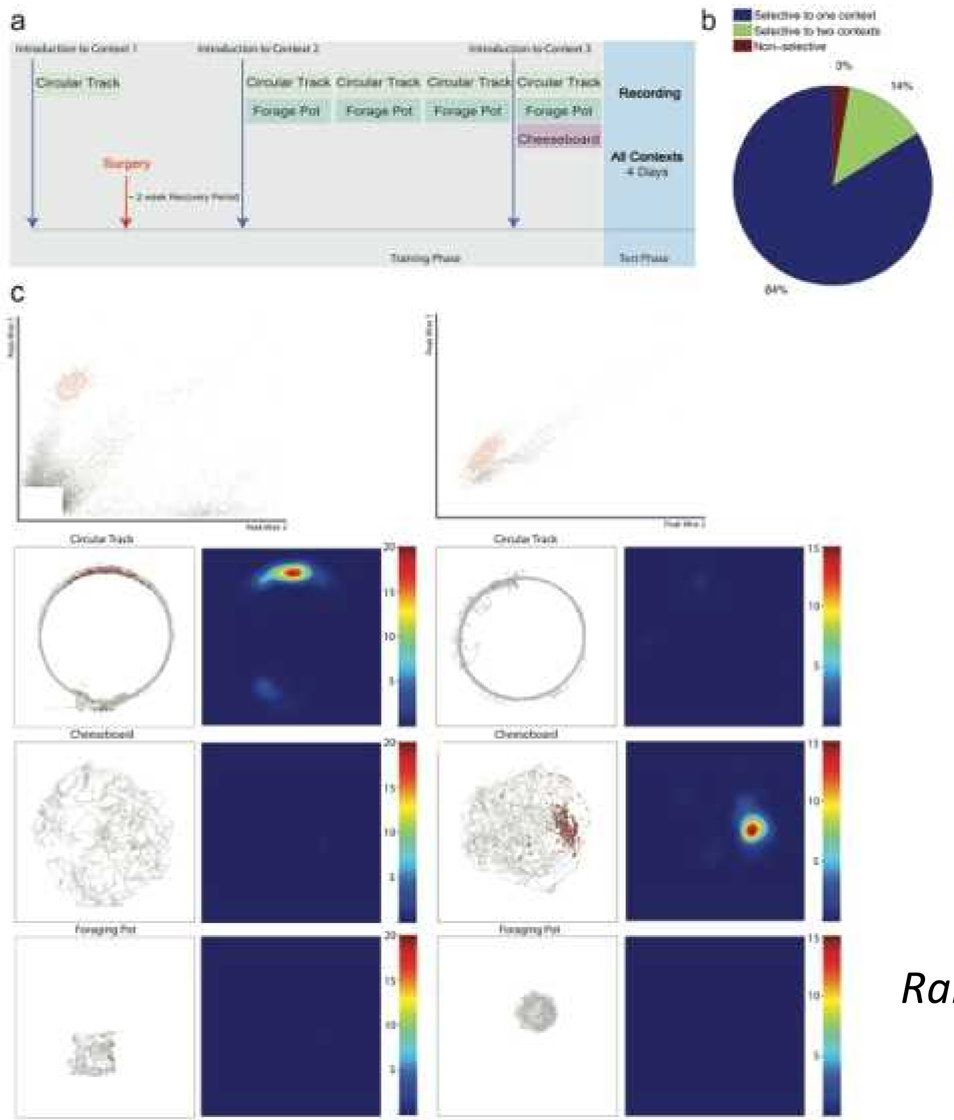


2000 synapses
25% (500) active
required to fire
20% (400) active on
average



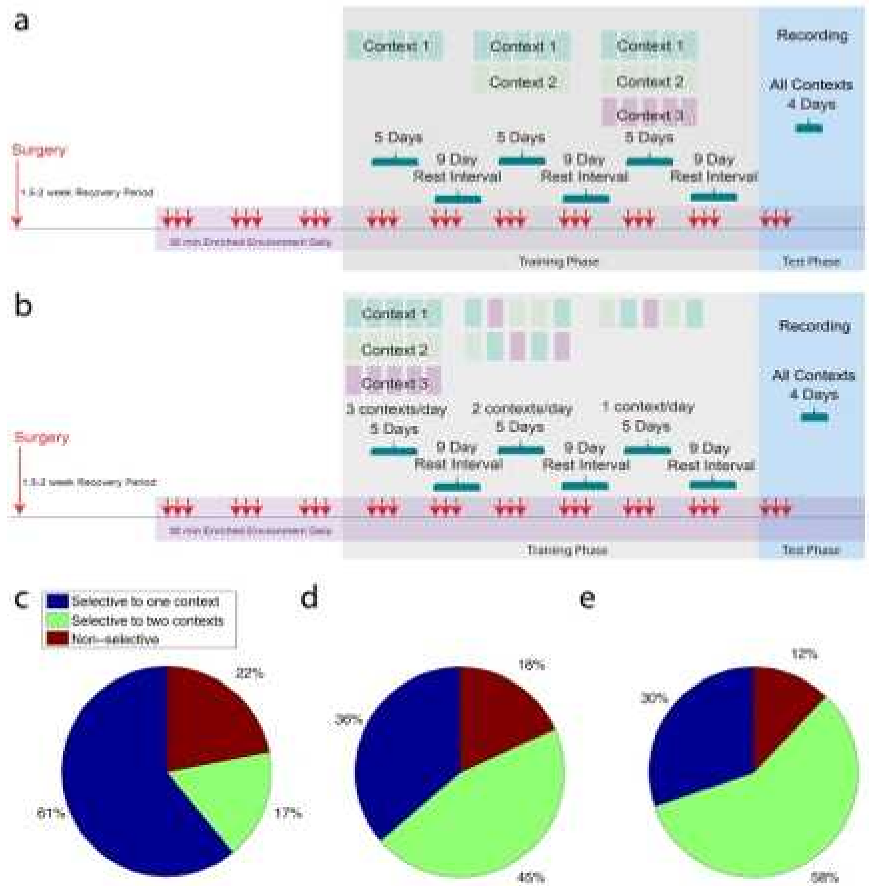
Li, Aimone, et al., PNAS 2012

Some biological evidence



Rangel et al., submitted

Non-neurogenesis animals have more selective neurons

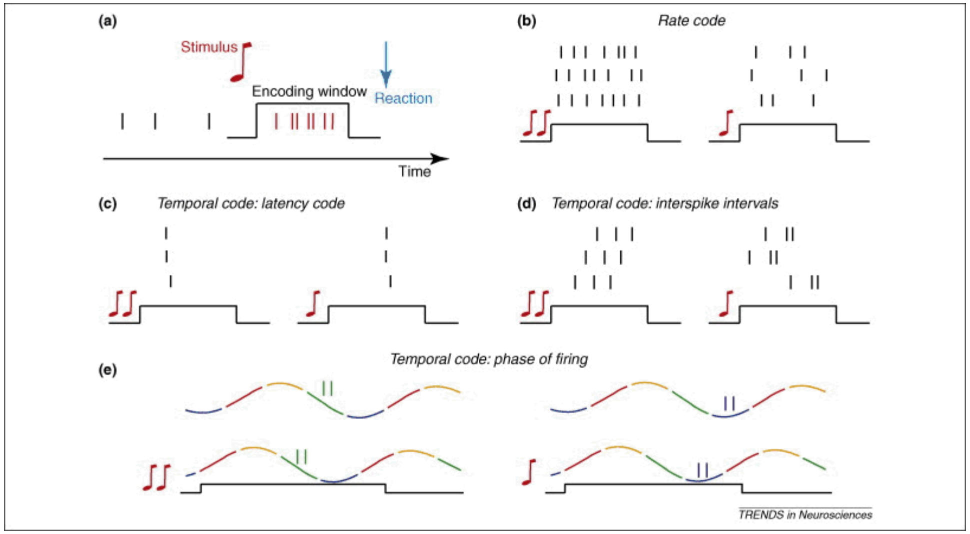


Rangel et al., submitted

What about timing?

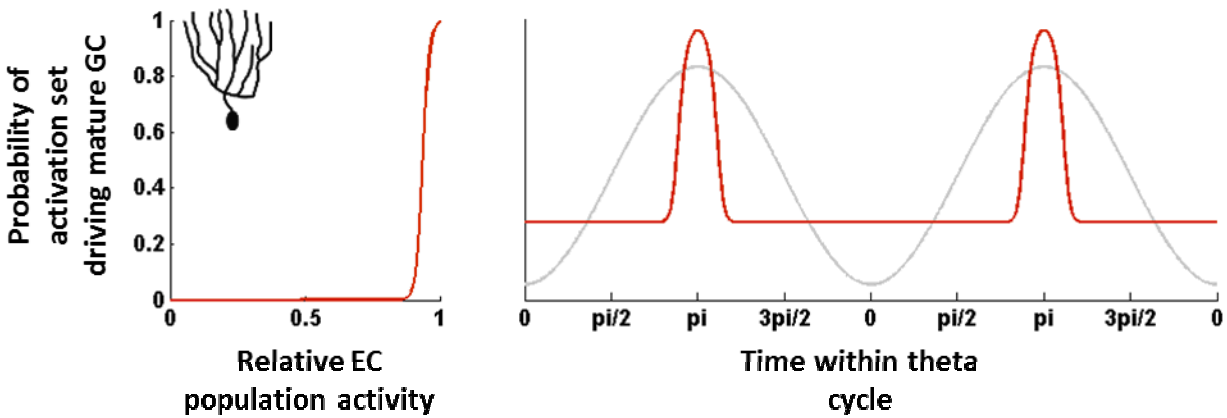
When neurons fire is often as important as how often they fire

- Sensory systems
  - Synchrony in responses
- Motor systems
  - Dynamical representation of cognitive state
- Hippocampal phase precession
  - “When” within an oscillation corresponds to “where” within the place field

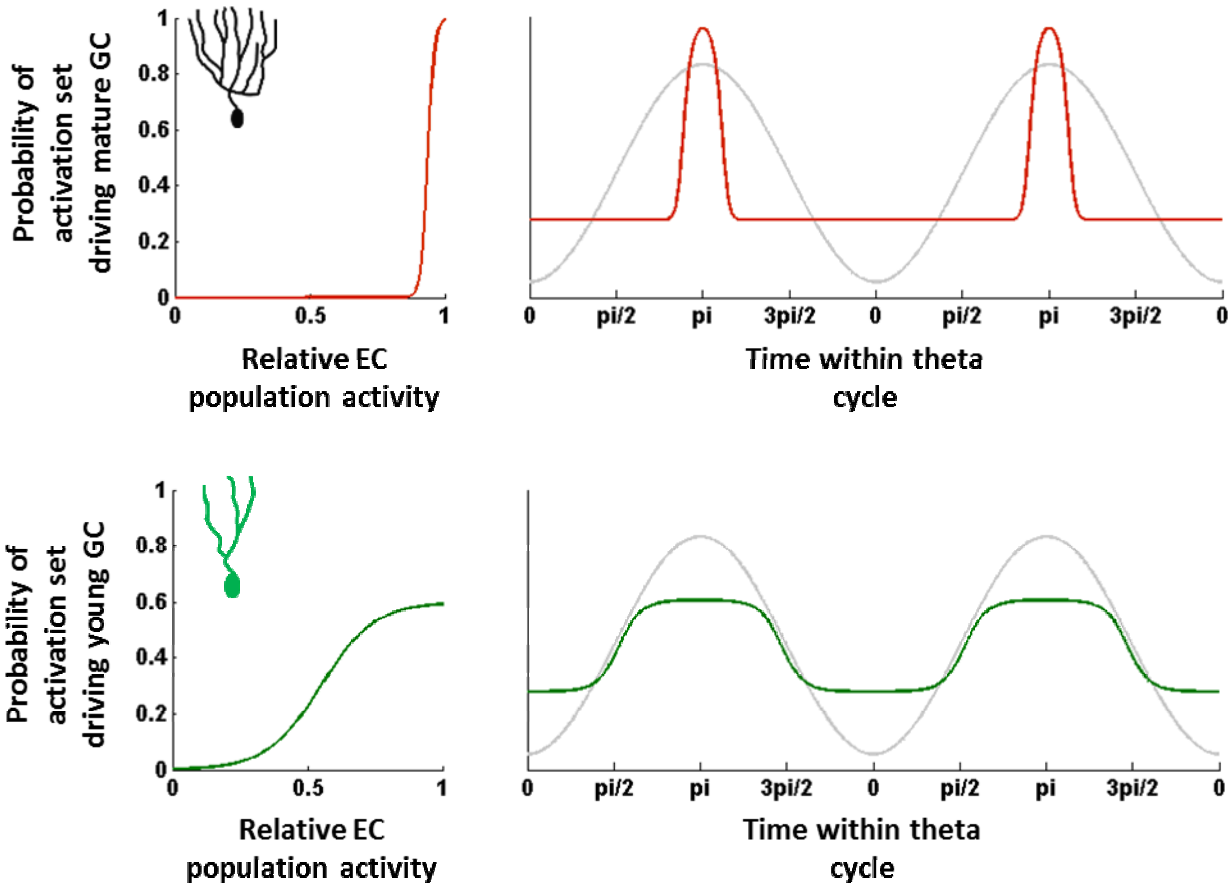


Panzeri et al., TINS, 2010

Tight tuning of GCs yields tight temporal tuning?



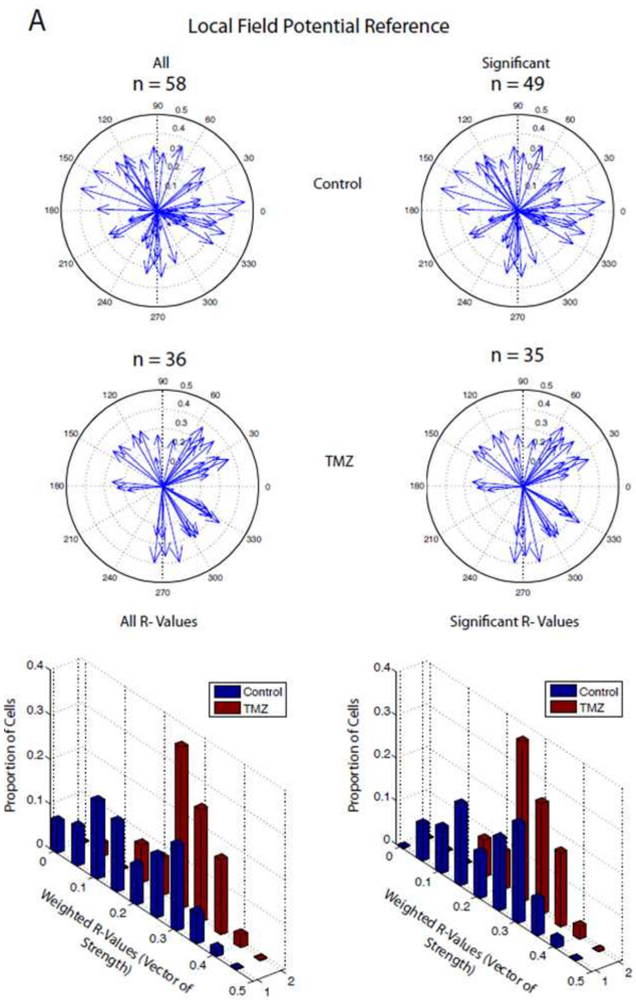
Broad tuning of GCs yields broad temporal tuning?



Rangel et al., submitted

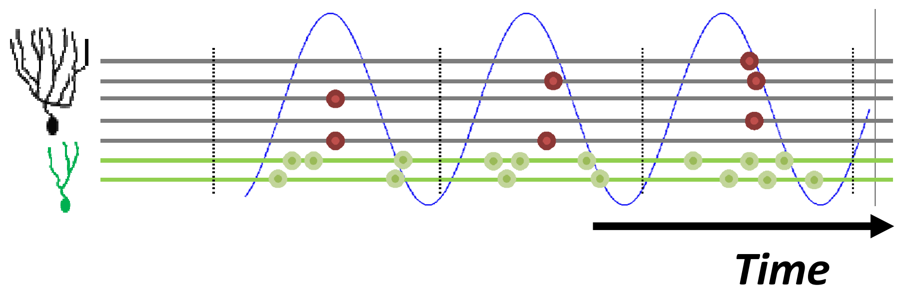
Some preliminary evidence

- TMZ and control rats with in vivo DG recordings
- Compare spikes of isolated GCs to local theta rhythm
  - *Prediction: young GCs would be phase incoherent; mature GCs would be phase coherent*
- TMZ animals show higher density of phase coherent (putative mature) neurons
- Control animals show mix of phase coherent (putative mature) and incoherent (putative young) neurons.



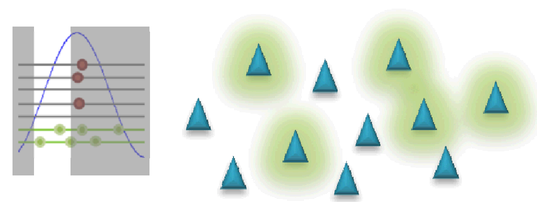
Rangel et al., submitted

What temporal new neuron coding could mean

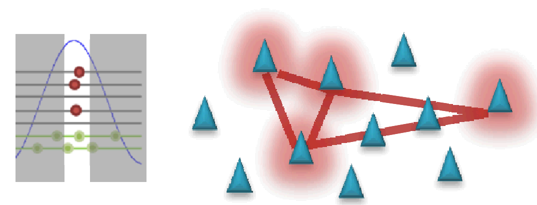


<u>Potential Impacts</u>

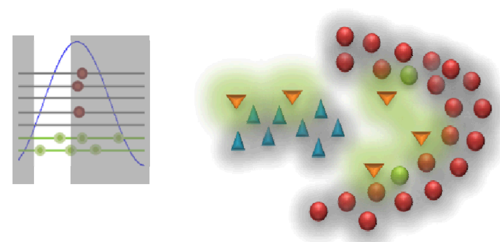
- Young neurons “prime” subset of CA3 population to entrain to inputs



- Synchronization of mature neurons to improve CA3 attractor formation



- Young neurons increase separation by activating feed-forward (in CA3) and feedback inhibition (in DG)



Rangel et al., submitted

Back to humans…

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ARTICLES

Neurogenesis in the adult human hippocampus

Peter S. Eriksson[1,4], Ekaterina Perfilieva[1], Thomas Björk-Eriksson[2], Ann-Marie Alborn[1], Claes Nordborg[3], Daniel A. Peterson[4] & Fred H. Gage[4]

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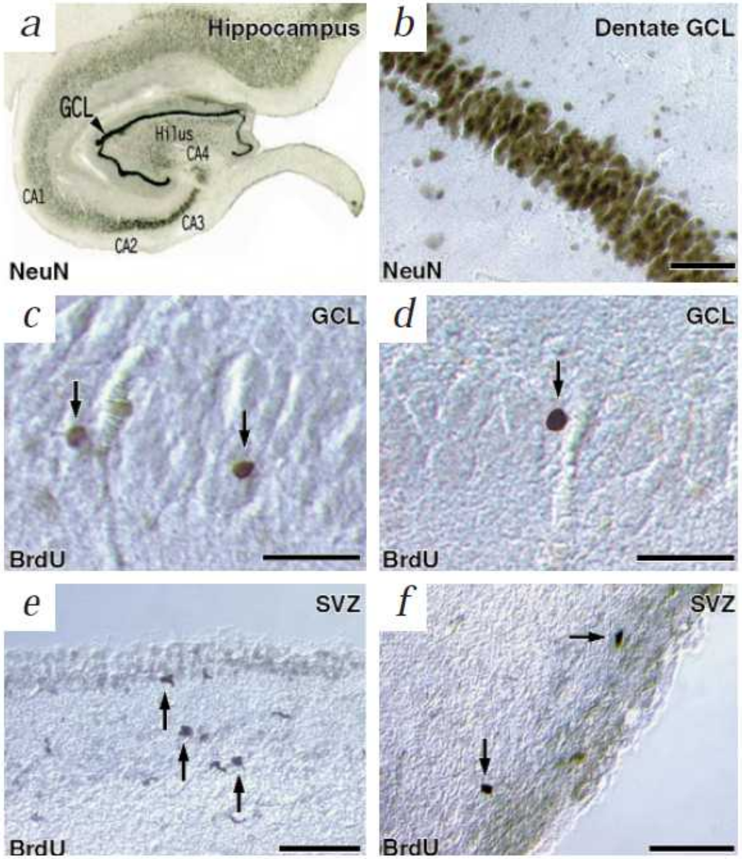
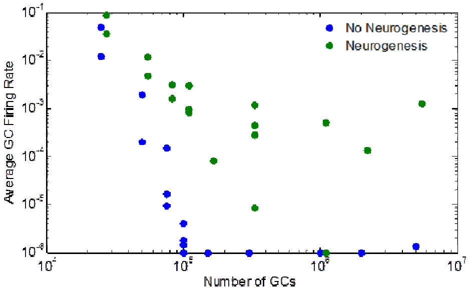


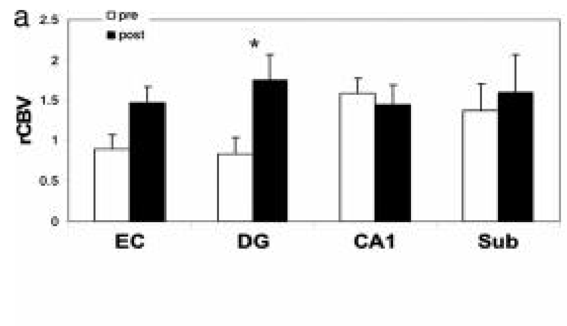
Are there enough?

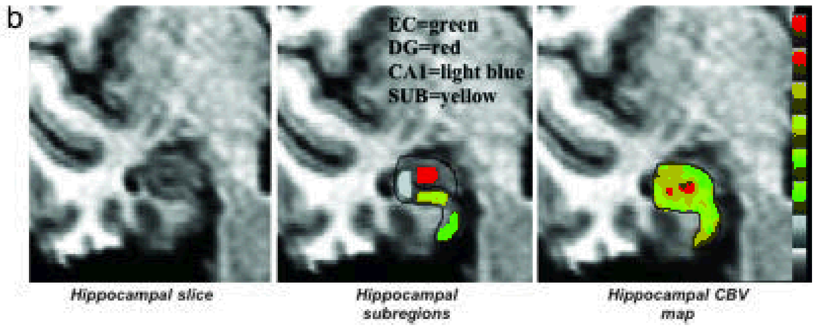
Model data suggests that fewer are necessary as networks get progressively larger



Looking at neurogenesis in humans

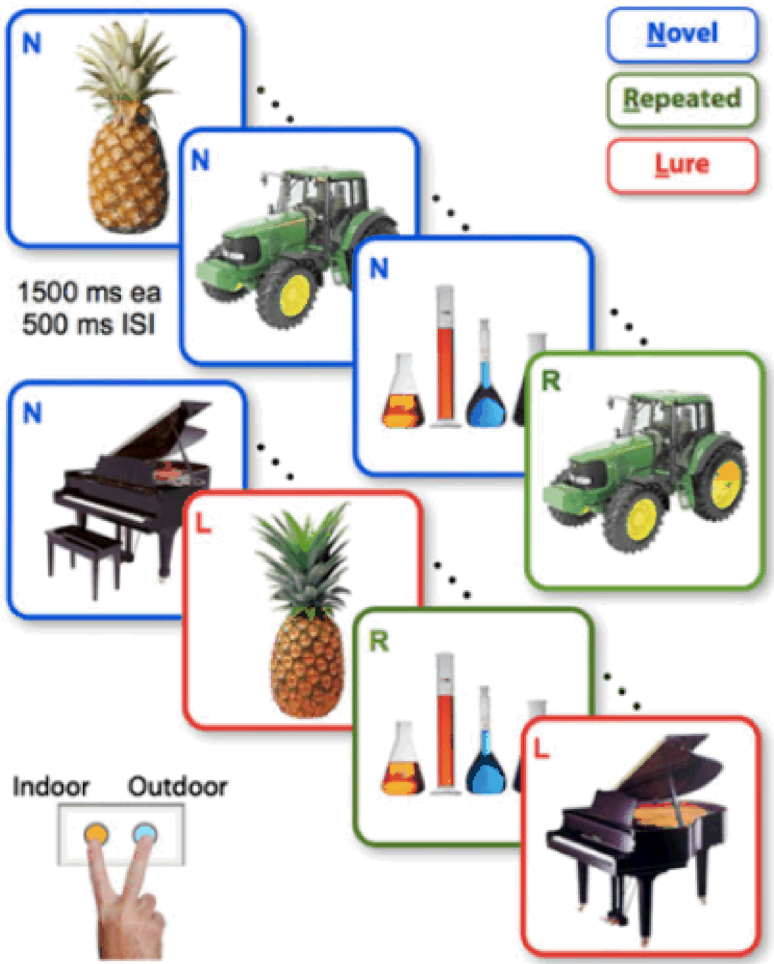
- Only a few correlative methods
  - CBV MRI measurements
  - Other MRI signatures
  - Postmortem histology
- Conditions with likely neurogenesis decreases
  - Aging
  - Depression
  - Chemotherapy

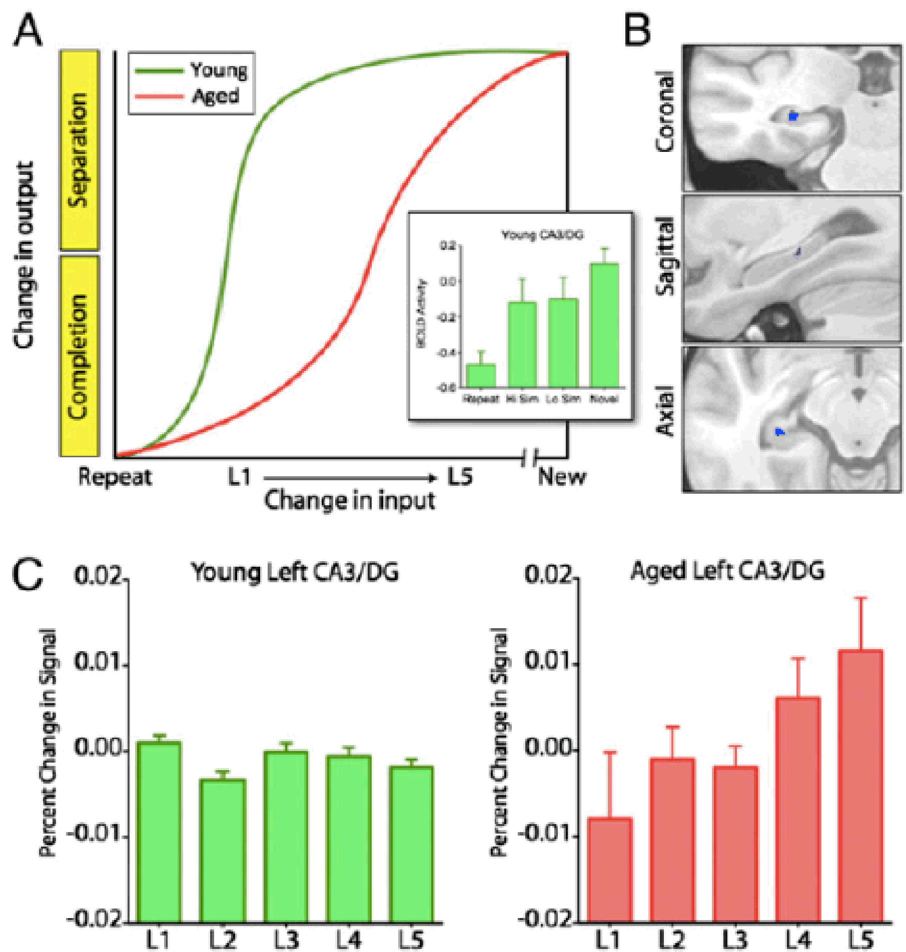




Pereira et al., PNAS 2007

What human tasks would be affected?





Yassa et al., PNAS 2011

Conclusions

- Computational models are increasingly able to overcome scaling challenges
- Human neurogenesis is likely relevant, question is now what tasks are best to examine it
- “Memory resolution” lens is useful for describing DG and neurogenesis function

Thanks!

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