SAND2014-3489C

Revisiting a Model: Continually Reassessing the Computational Role of Adult Neurogenesis

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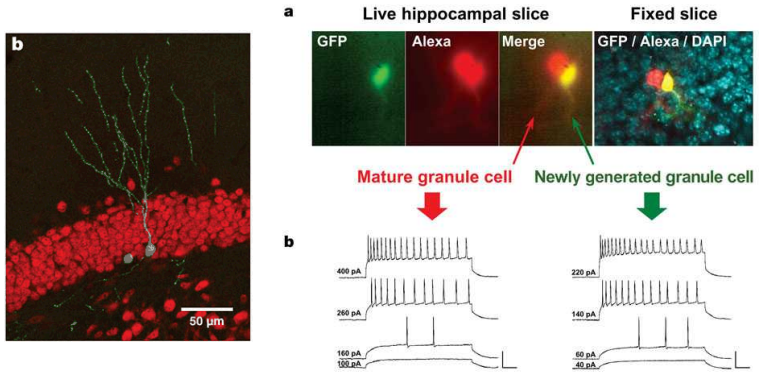
Time and Context

Computation of Neurogenesis 10 years ago…

Neurogenesis

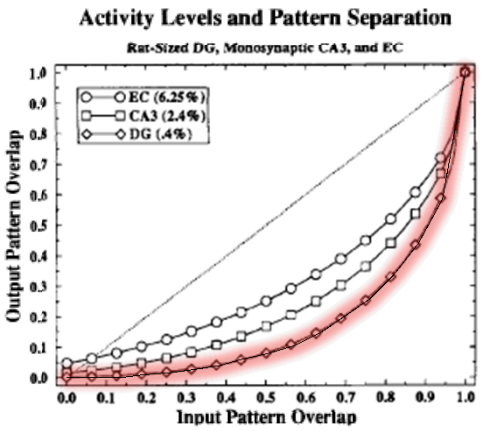
- Present in Humans
- Physiologically Active
- Behaviorally regulated



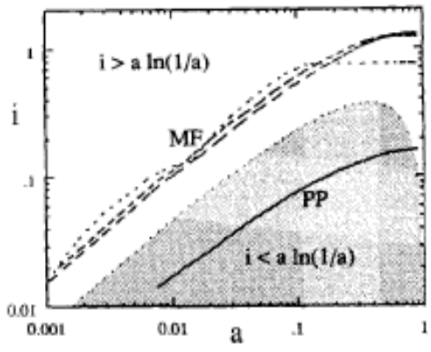
van Praag, Schinder, et al, 2002

Dentate Gyrus

- Conjunctive encoding
- Pattern separation
- Sparse, powerful outputs

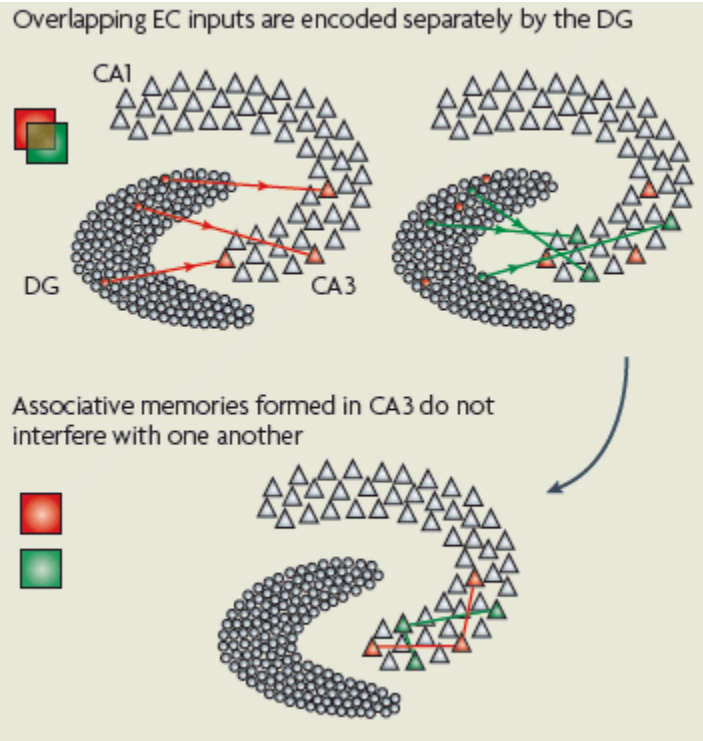


O'Reilly, McClelland, 1994



Treves, Rolls, 1992

Pattern Separation in DG



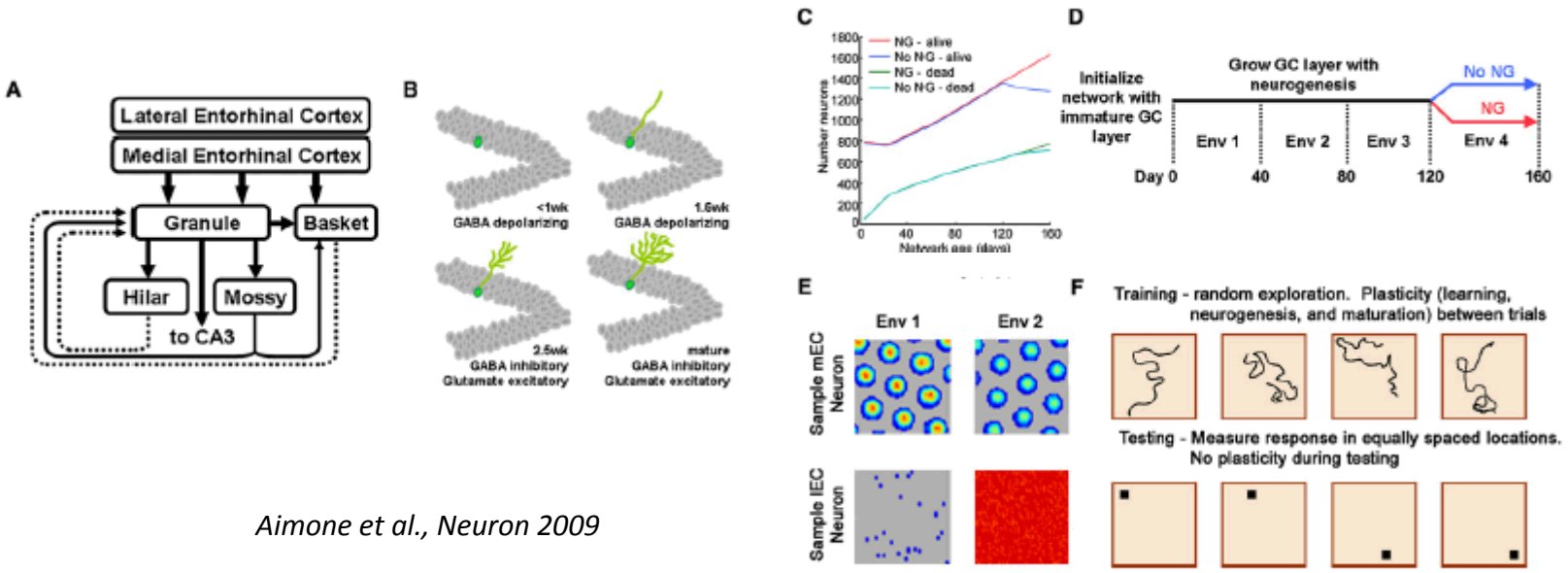
Deng, Aimone, & Gage, Nat Rev Neuro 2010

So how do new neurons affect this?

Neuron
Viewpoint

Computational Influence of Adult Neurogenesis on Memory Encoding

James B. Aimone,[1] Janet Wiles,[2] and Fred H. Gage[1,*]
[1]Laboratory of Genetics, Salk Institute for Biological Studies, La Jolla, CA 92037, USA
[2]School of Information Technology and Electrical Engineering, University of Queensland, Brisbane, Queensland 4072, Australia

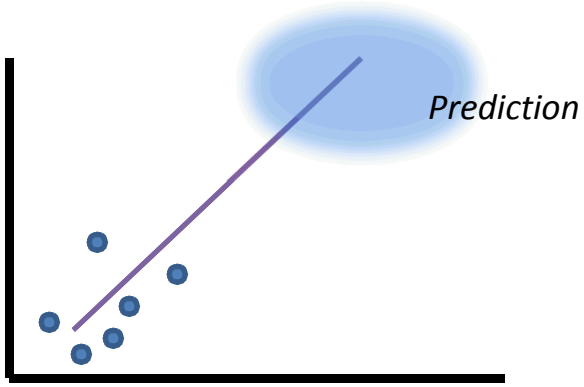


Aimone et al., Neuron 2009

Different types of model…

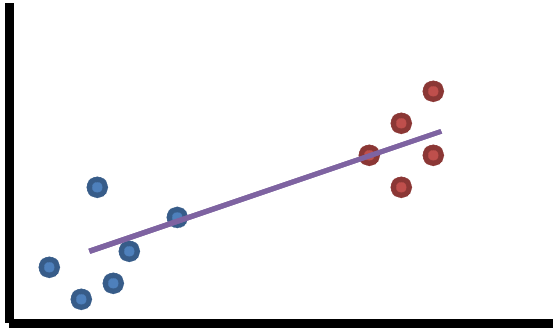
"Predictive" model

Extrapolate from low-level data points to predict what will be seen at a systems or behavior level



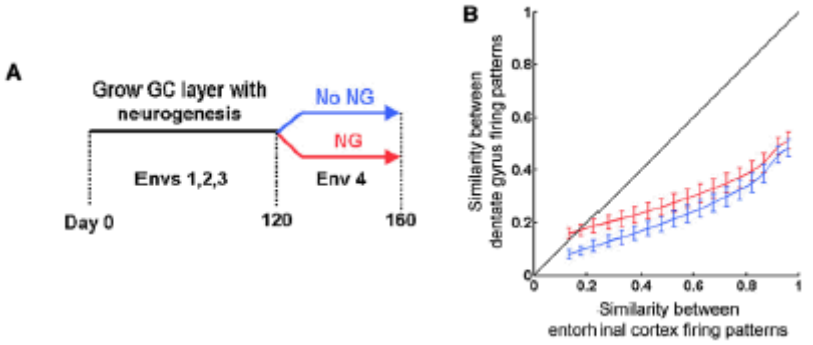
"Explanatory" model

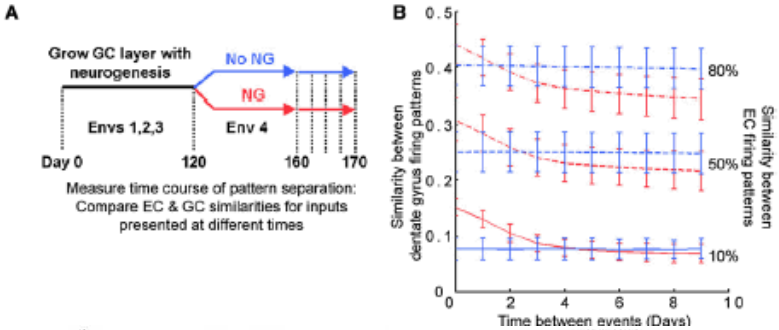
Interpolate between low-level data points and those at a systems or behavior level to explain relationship between scales

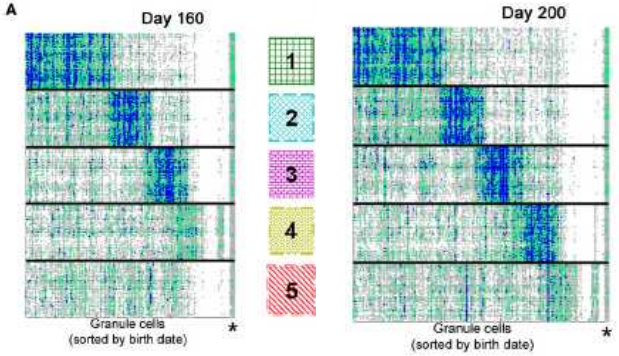


Three predictions at the time…

- Pattern Integration
- Temporal Separation
- Dentate Specialization







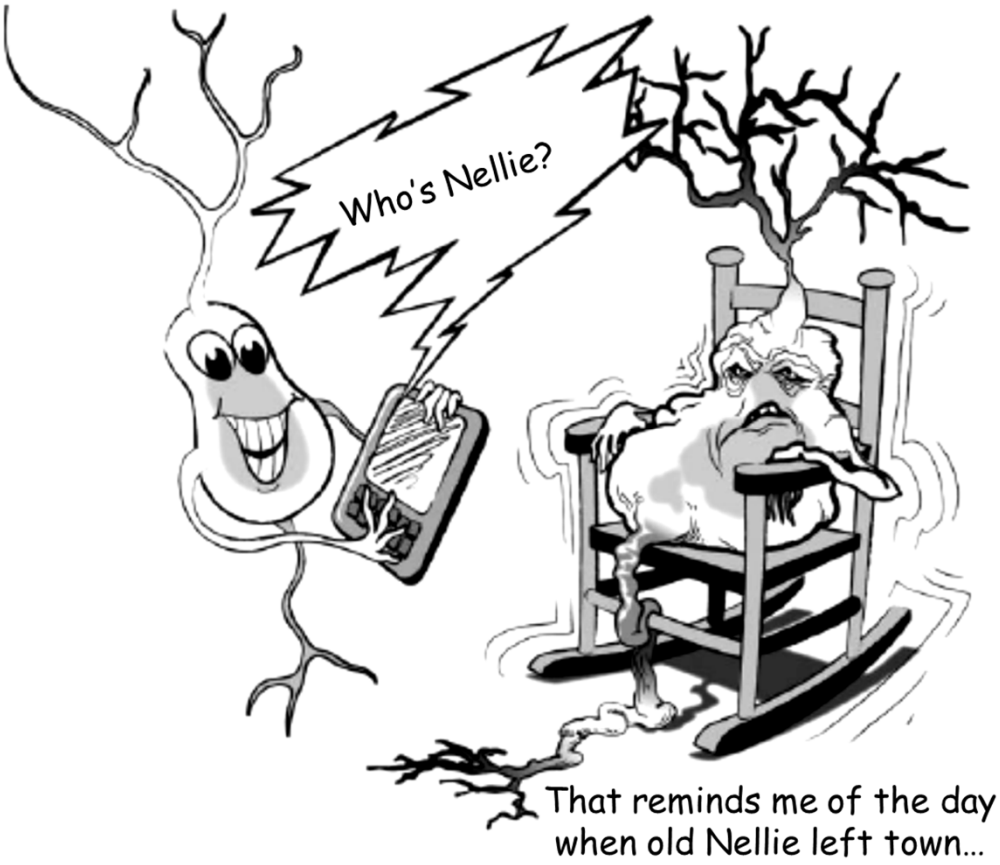
Aimone et al., Neuron 2009

So how do these look five years later?

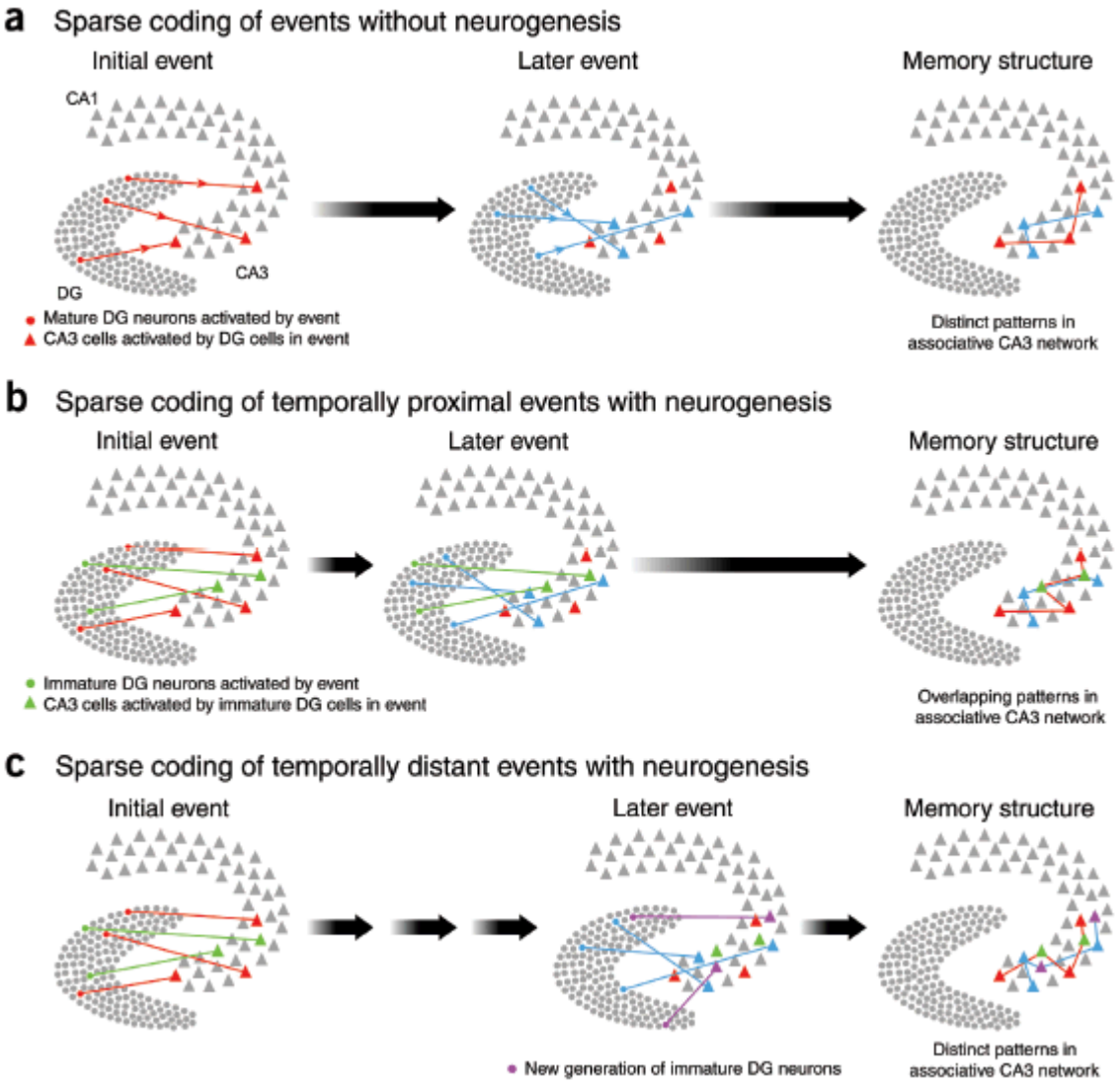
Overall what has changed

- More details on neural physiology
  - Generally consistent with model
- Improved knockdown methods
  - Transgenic mice
  - Temozolomide (TMZ)
- Focused behavior tasks
  - i.e., Tim Bussey pattern separation task
- Increasing focus on in vivo DG physiology

Temporal Separation
Five years later



Adapted from
Aimone, Deng and Gage, Hippocampus, 2011



Aimone et al., Nat Neuro 2006

Time coding evidence?

- Long temporal associations in DG…

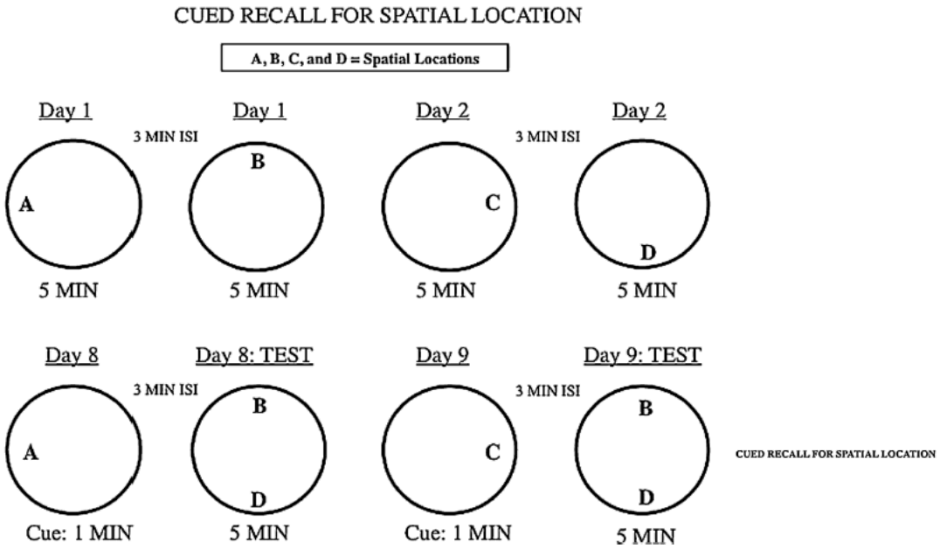
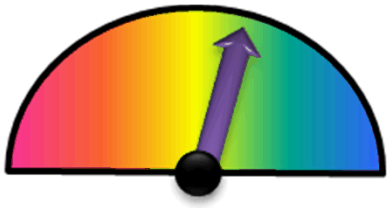
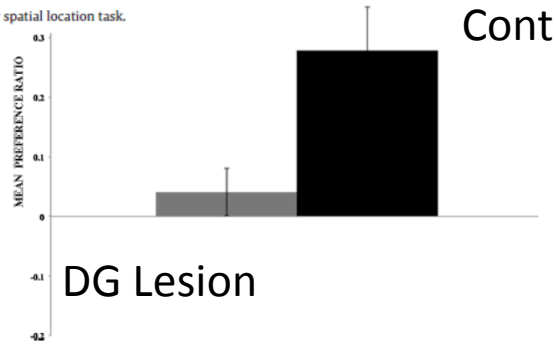


Fig. 1. Schematic representation of behavioral procedures for cued recall for spatial location task.

Morris et al., Behav Brain Res,2013



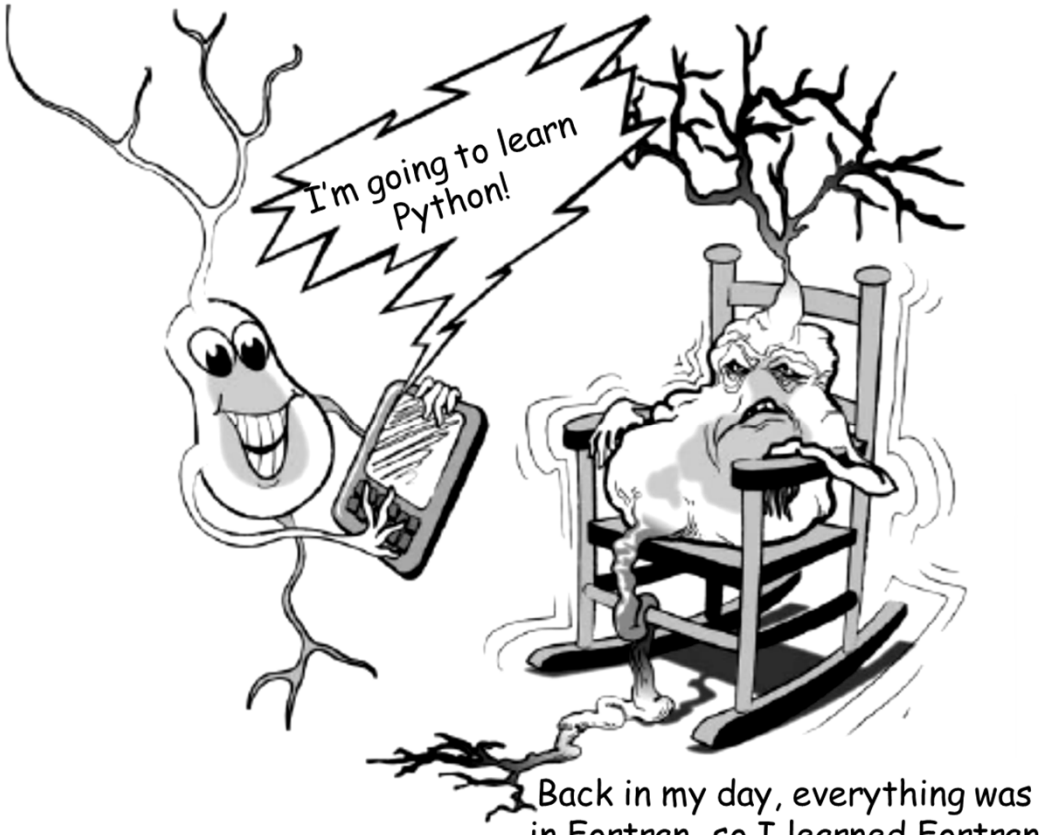
Needs to be studied…



Control

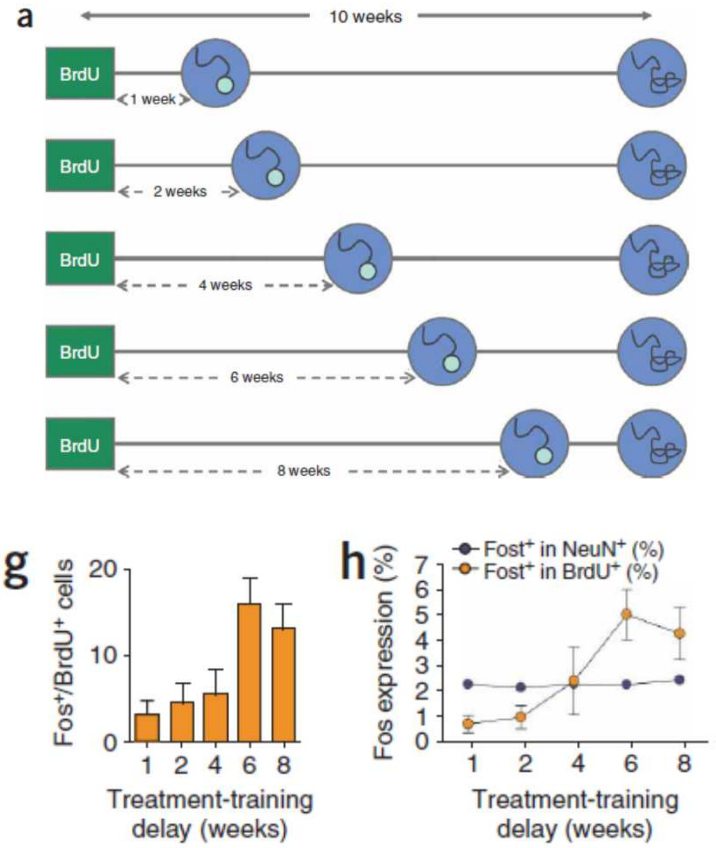
DG Lesion

New Neuron Specialization
Five years later

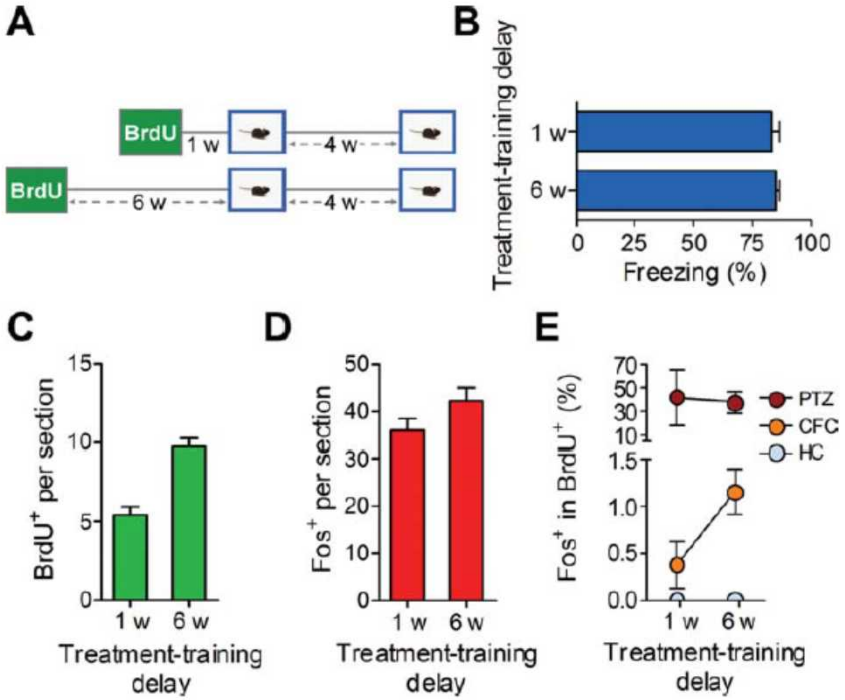


Adapted from
Aimone, Deng and Gage, Hippocampus, 2011

Do new neurons “specialize”? – Immediate early gene evidence

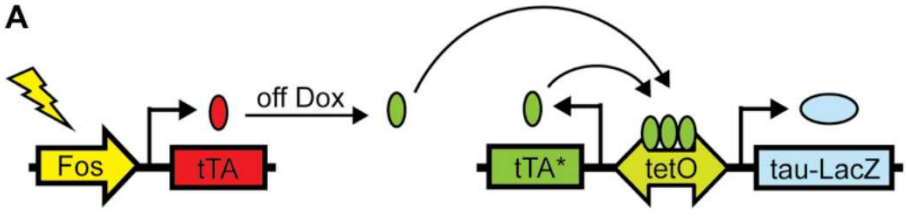


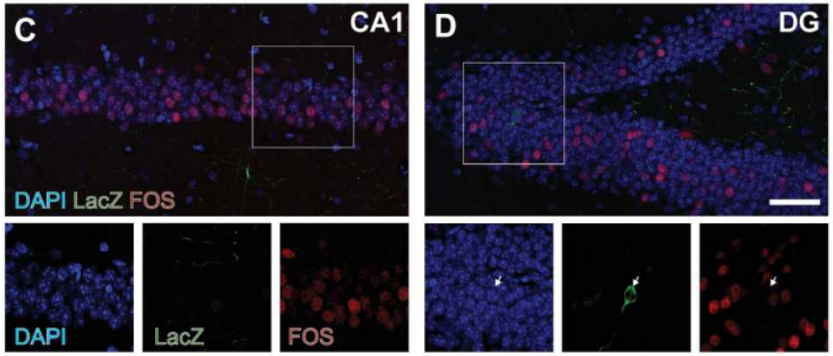
Kee et al., Nat Neuro 2007

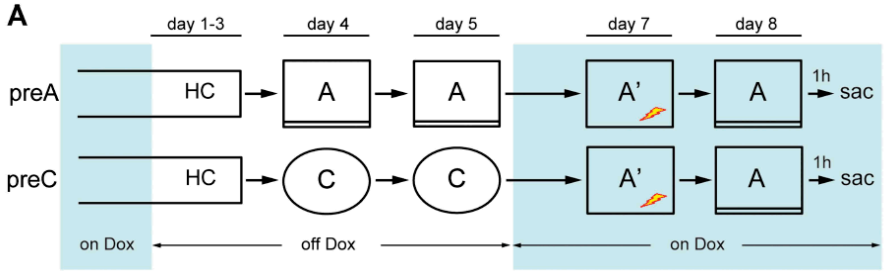


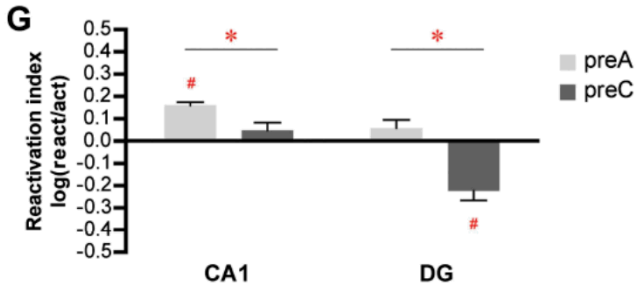
Stone et al., Hippocampus2011

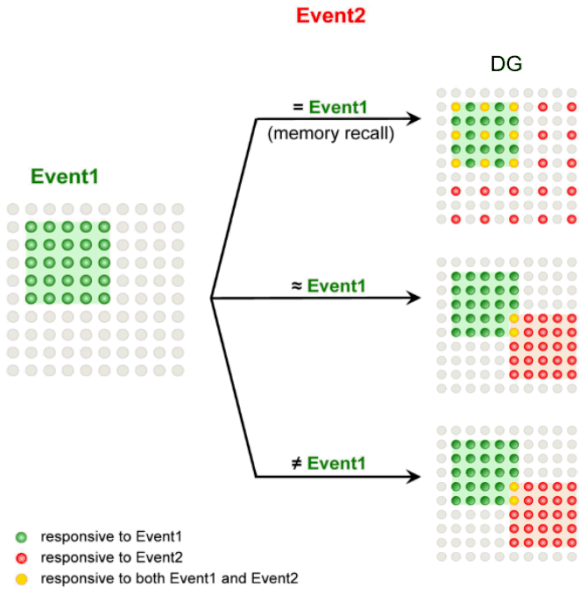
Do new neurons “specialize”? – DG tet-tag evidence





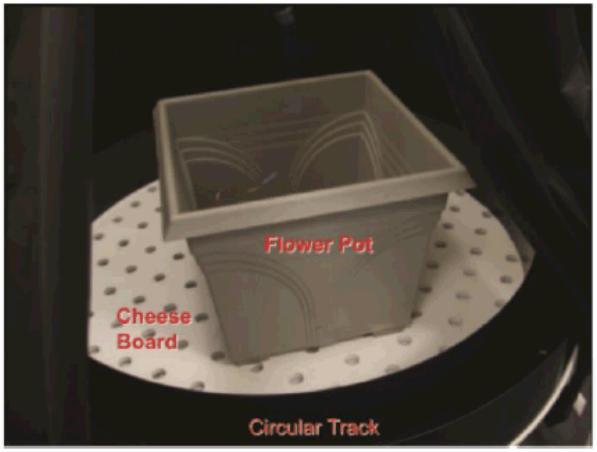


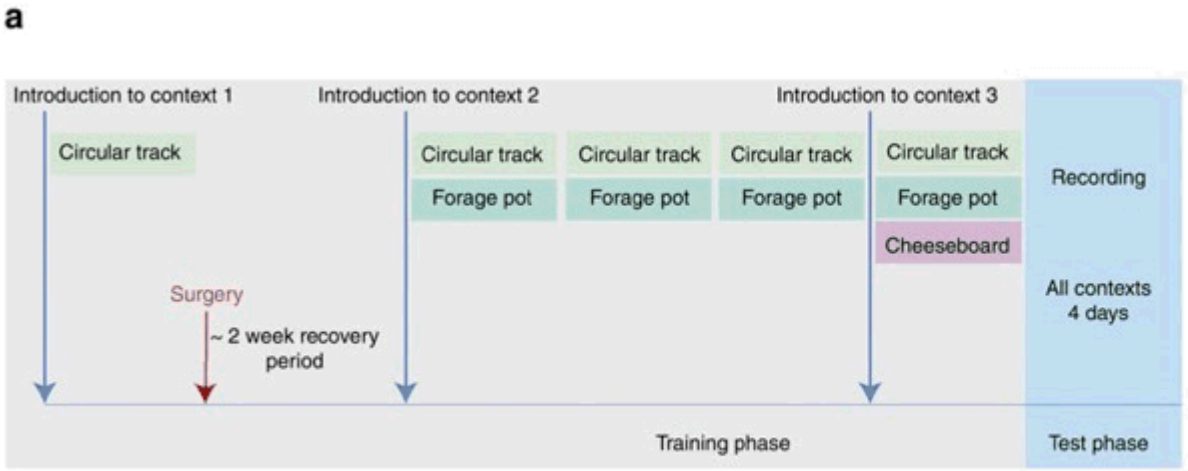


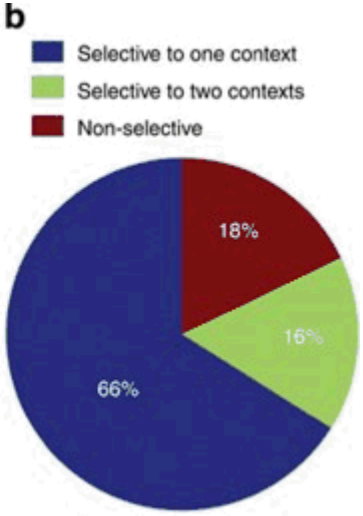


Deng et al., eLife 2013

Do new neurons “specialize”? – In vivo physiology evidence

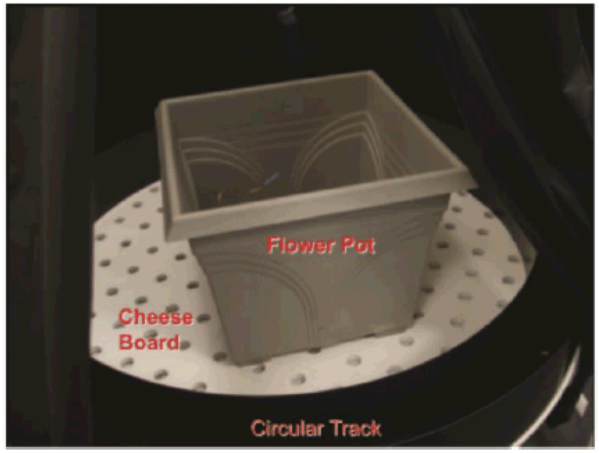


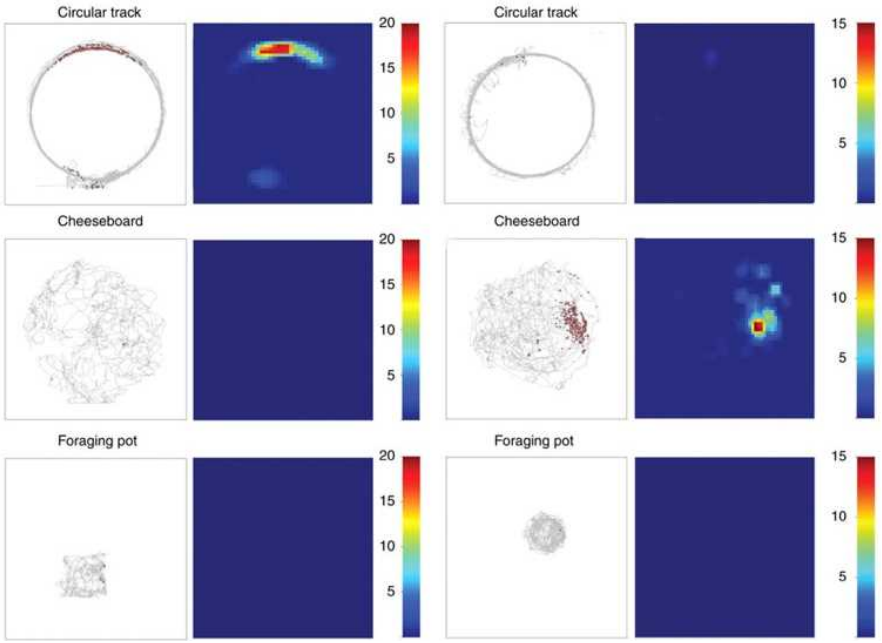




Rangel et al., Nat Comm 2014

Do new neurons “specialize”? – In vivo physiology evidence





Rangel et al., Nat Comm 2014

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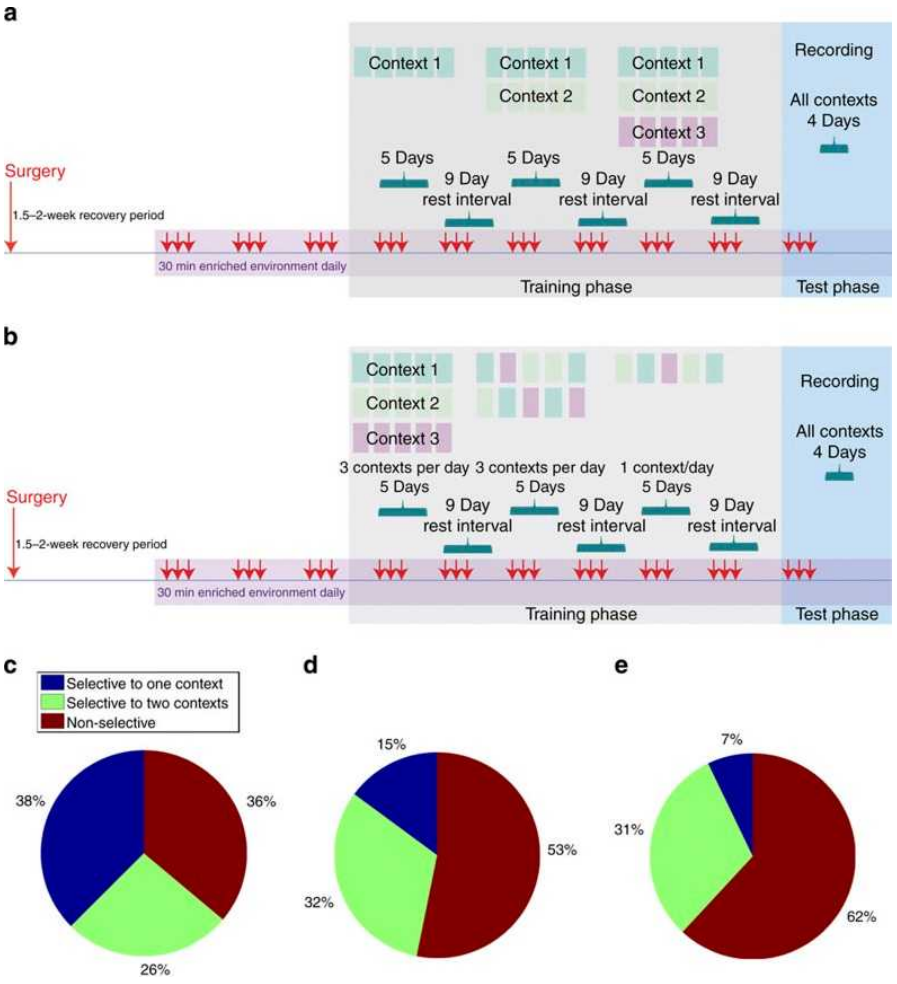
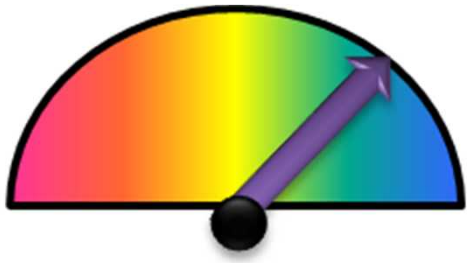


Rangel et al., Nat Comm 2014

Separated Simultaneous TMZ (NG knockdown)

Do new neurons “specialize”? - Overview

- IEG studies suggest some specialization, though timing and extent varies from study to study
- Whole DG cross temporal labeling (tet-tag) suggests complex overall mechanism
- In vivo physiology of DG shows some cross temporal specialization, though young neurons are not specifically identified



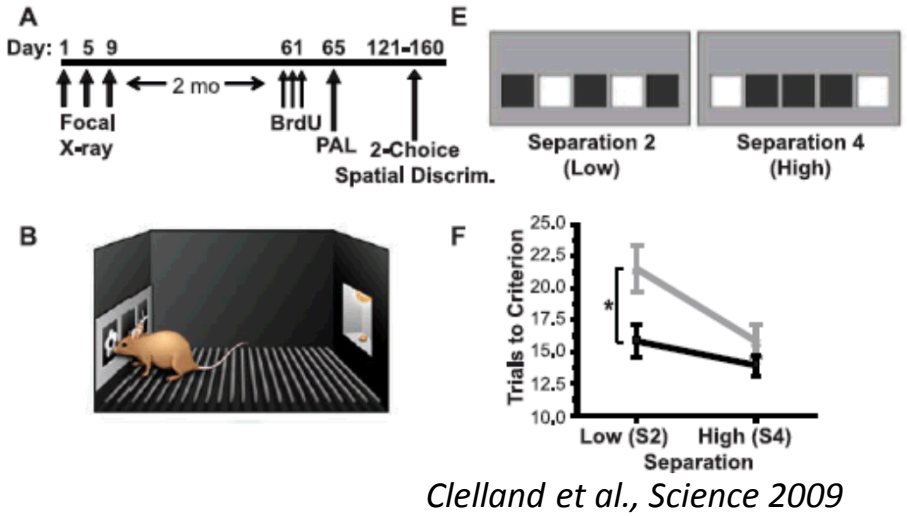
Looking good, but somewhat complex results

Pattern Integration
Five years later

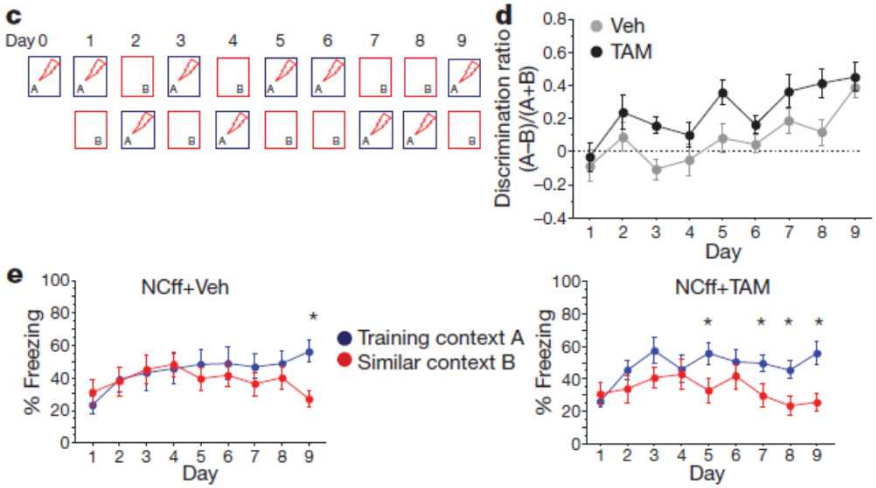
Adapted from
Aimone, Deng and Gage, Hippocampus, 2011

Does NG Perform "Integration"?– Behavioral Evidence

- Spatial Discrimination routinely shown to be dependent on neurogenesis
- Increasing neurogenesis improves discrimination
- Numerous functional imaging studies in humans highlight DG's role in pattern separation

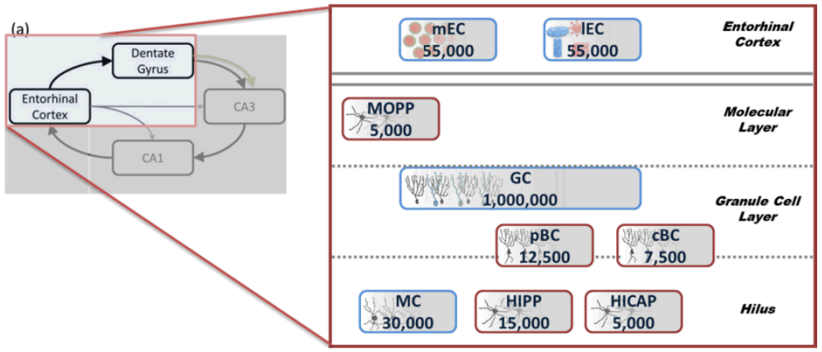


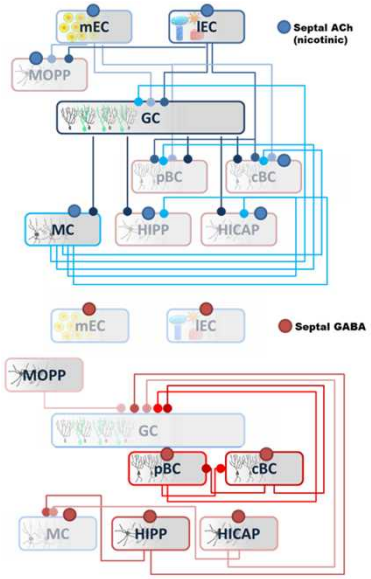
Clelland et al., Science 2009



Sahay et al., Nature 2011

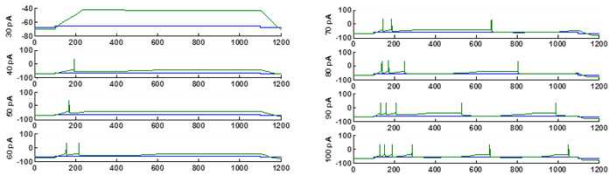
Does NG Perform “Integration”?– More realistic computational modeling



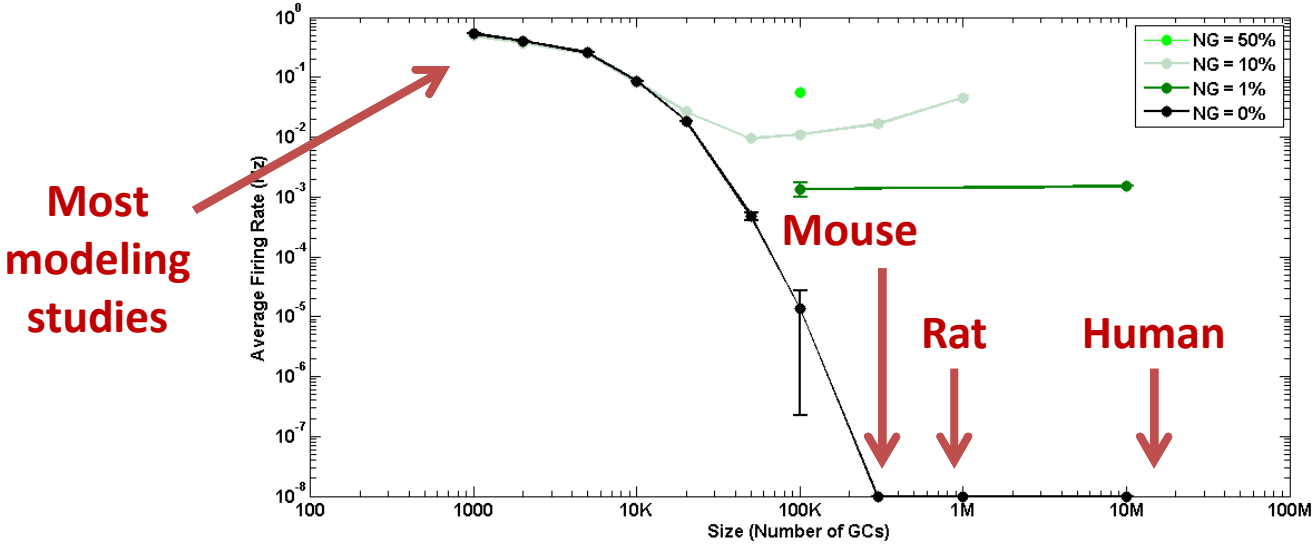


Physiology data

Modeled neuronal dynamics

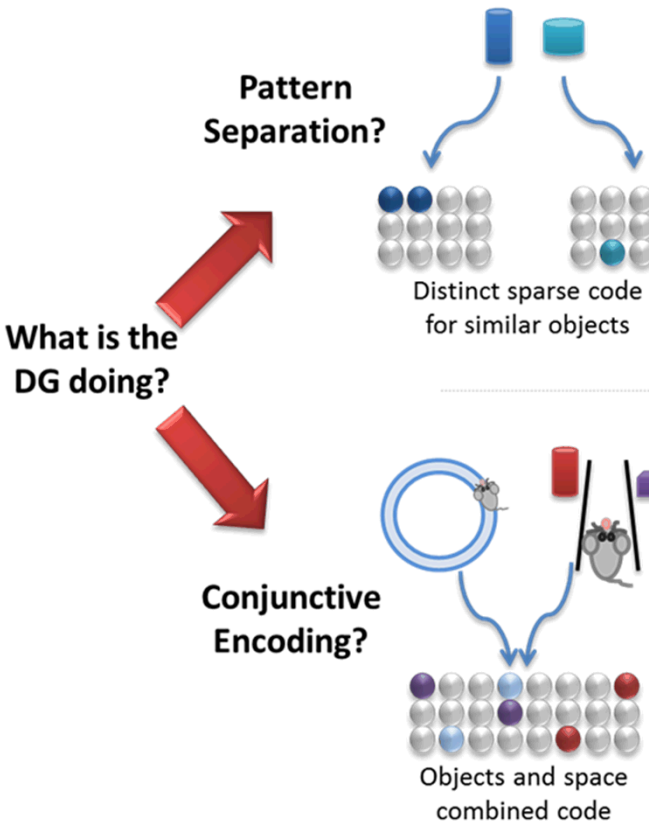


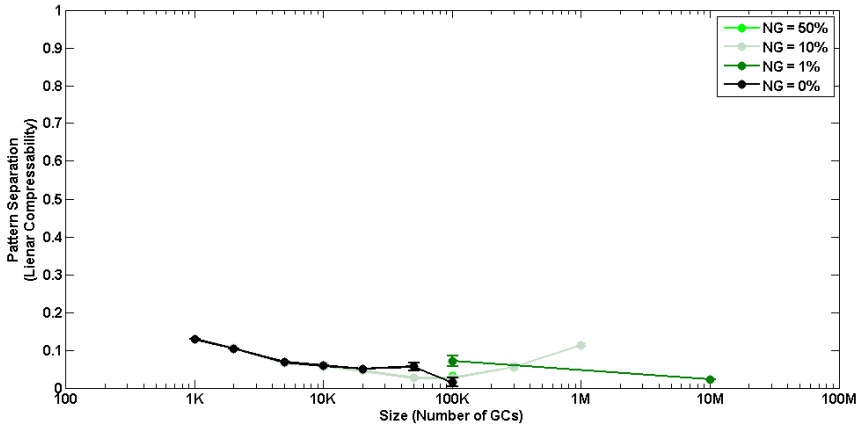
Function of neurogenesis is scale dependent…

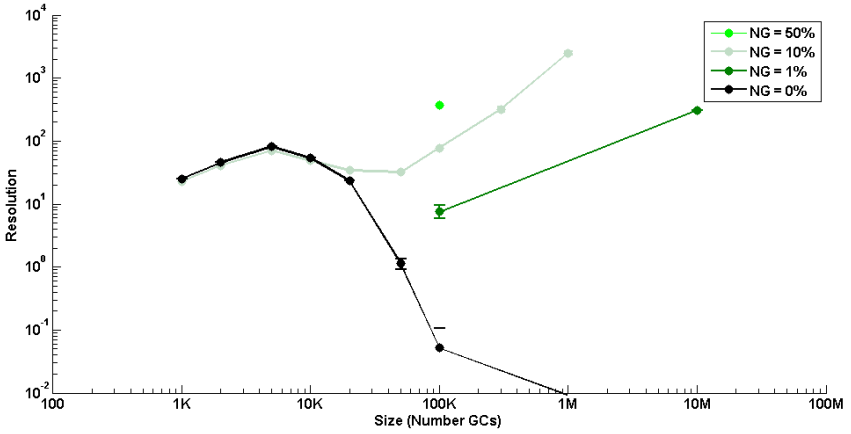


- Neurogenesis networks show activity to novel information at much higher scales
- As we approach human scales, mature neurons appear essentially silent in response to novel information
- Signal (immature) to noise (mature) is amplified in larger networks

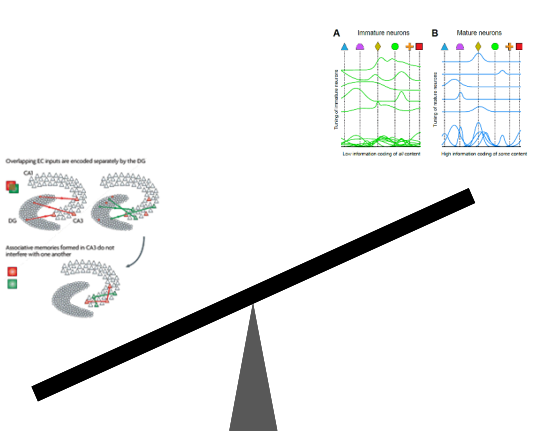
Neurogenesis maintains compressibility and increases total representation





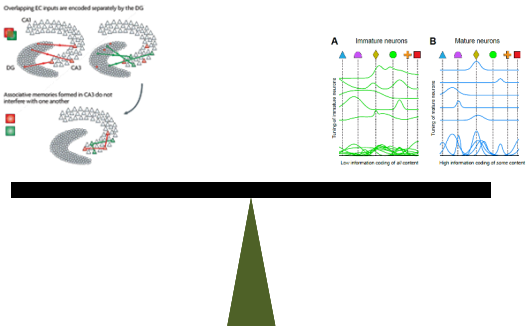


Neurogenesis strikes a balance between pattern separation and memory information content



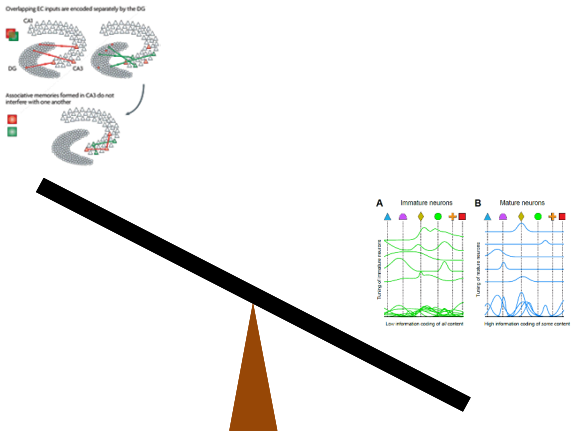
No neurogenesis yields very little activity

DG representations are separate but very sparse



Neurogenesis increases activity while preserving separation

DG representations increase their resolution but avoid interference

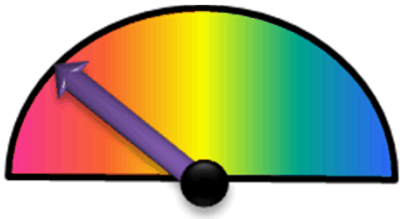


Increasing activity directly ruins pattern separation

DG representations are dense and informative but potentially interfere with each other

Integration Evidence – Overview

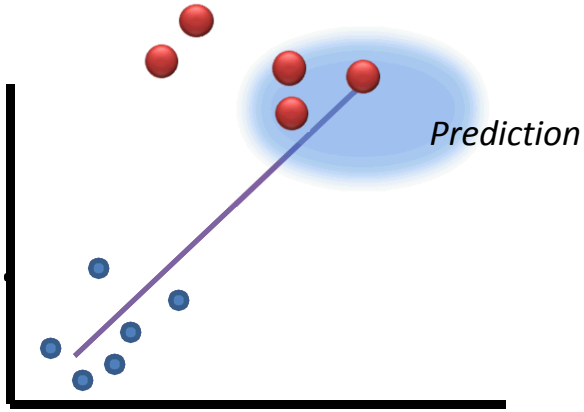
- Behavior strongly indicates new neurons are required for pattern separation
- Higher resolution modeling shows new neurons increase encoding without "integration" effect
- How brain compensates for loss of new neurons is big question



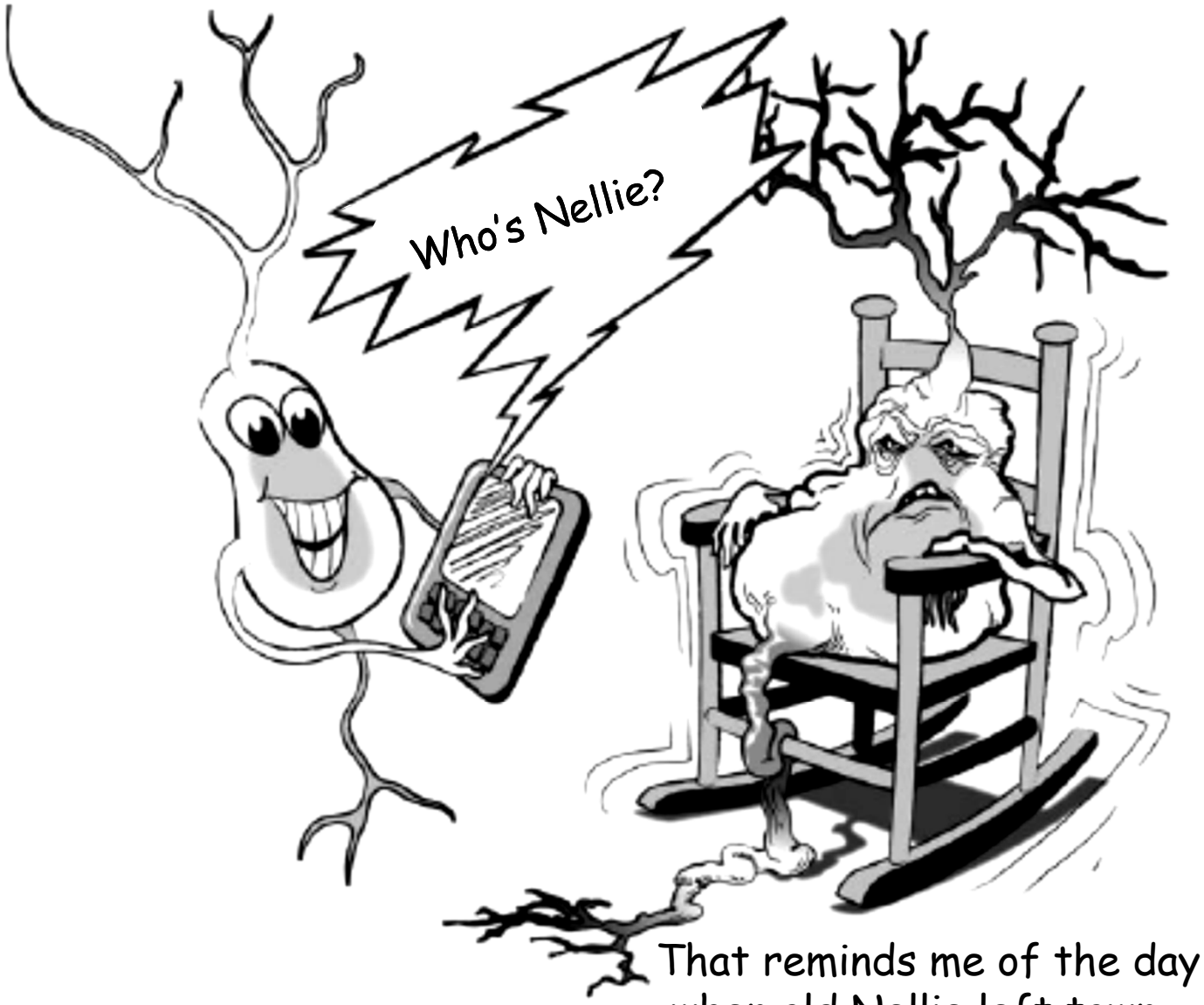
Not looking that good in the form presented

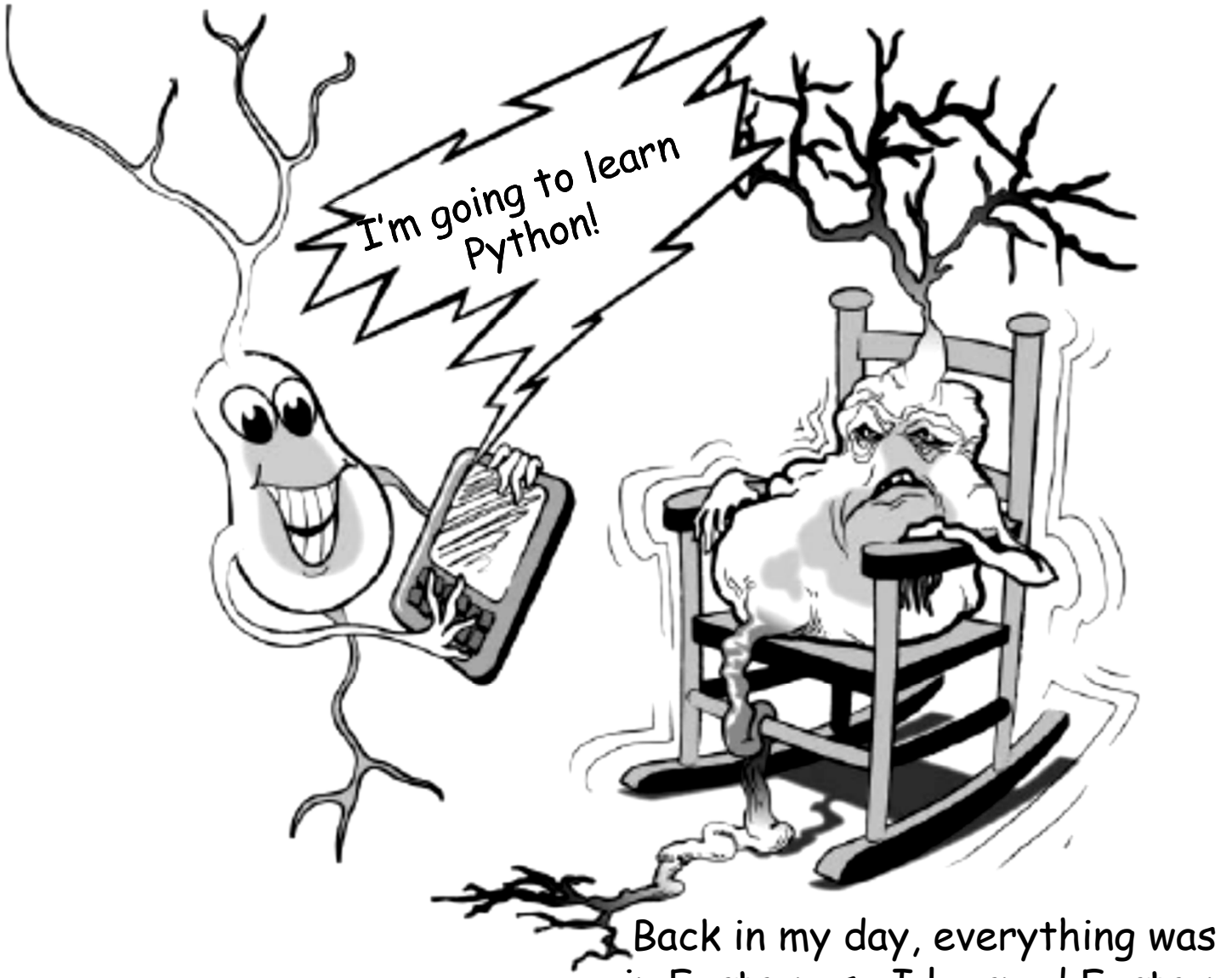
So what next?

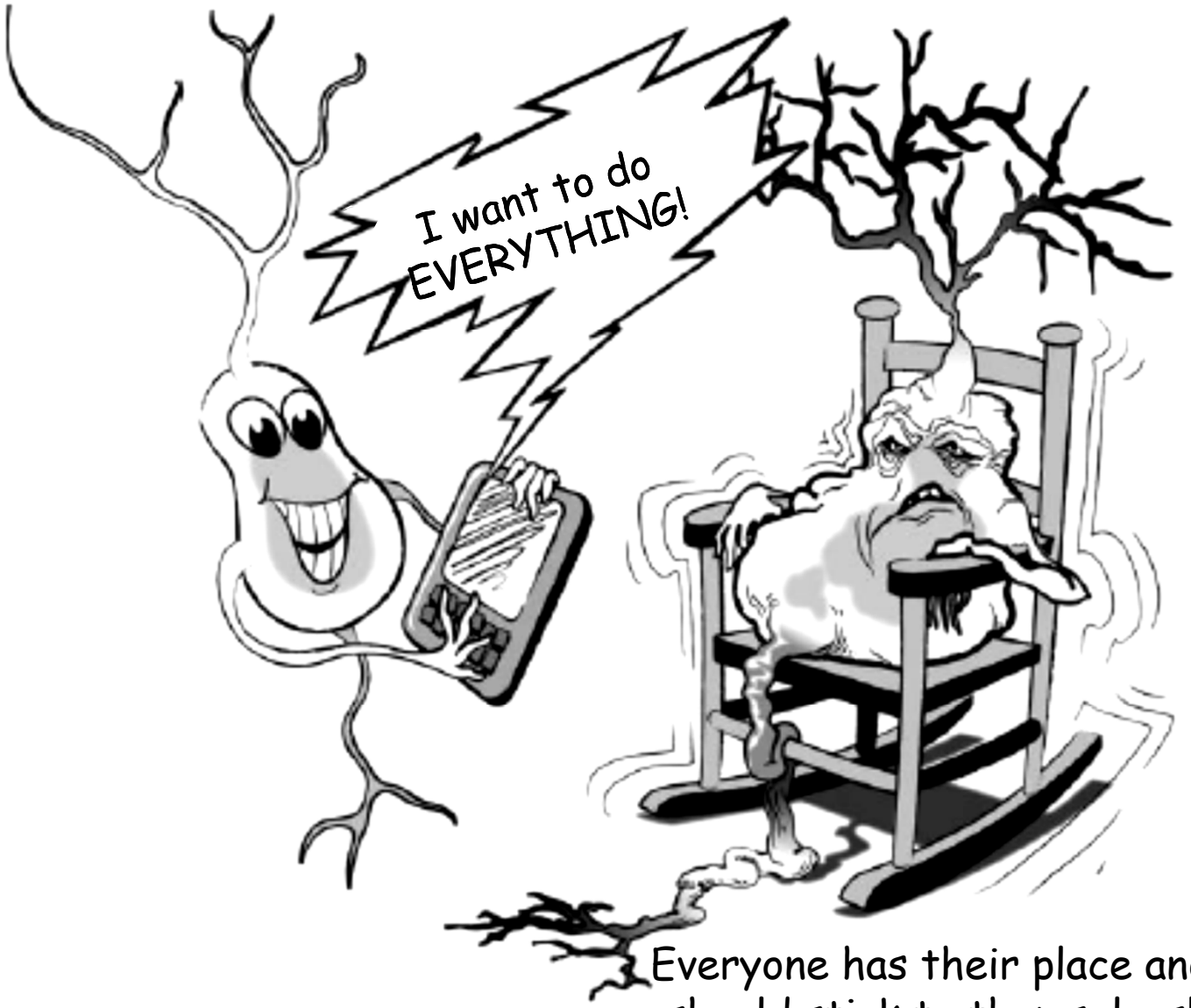
- Always good to revise models over time
  - If there is new data or new capabilities, never hurts to look again…
- Compensation and neurogenesis knockdowns
  - Big question regarding behavior…
- Focused in vivo physiology
  - Hard to see how single neurons map to population functions



Questions?


Who's Nellie?
That reminds me of the day when old Nellie left town…


I'm going to learn Python!
Back in my day, everything was in Fortran, so I learned Fortran



Everyone has their place and should stick to themselves!