Role of dentate gyrus adult-born neurons in hippocampus-dependent learning and memory

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1.Introduction

Neurogenesis occurring in adult animals including humans is a widely accepted idea nowadays. In mammals it is localized in two areas: the subventricular zone and the subgranular layer of the dentate gyrus in the hippocampus.

The hippocampal formation is vital for learning and memory processes such as spatial or contextual memory and new functional neurons are regularly incorporated to its trysinaptic circuit.

This review focuses on the role of adult-born neurons in these learning and memory mechanisms analyzing the available data and hypotheses.

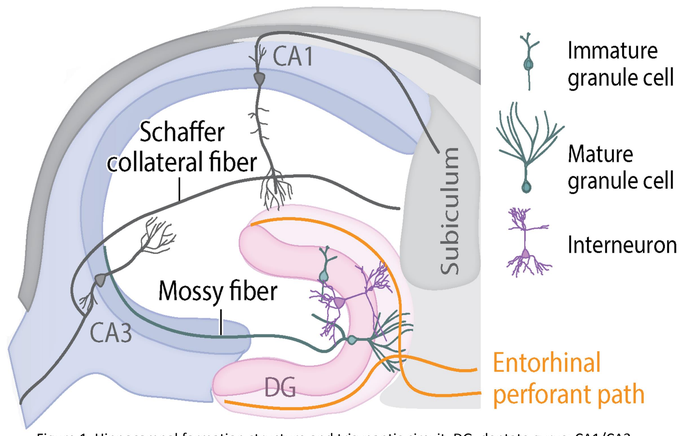


Figure 1. Hippocampal formation structure and trisynaptic circuit. DG, dentate gyrus; CA1/CA3, cornu ammonis 1/3. Modified from Christian et.al. Annu Rev Neurosci. 2014. 37:243-62.

2.Materials and Methods

Searches in scientific databases such as Pubmed, Scopus or Google Scholar were done to collect relevant scientific publications. Scientific literature was managed using the software Mendeley.

Keywords: adult neurogenesis, adult-born neurons, learning and memory.

3. Adult-born neuron maturation

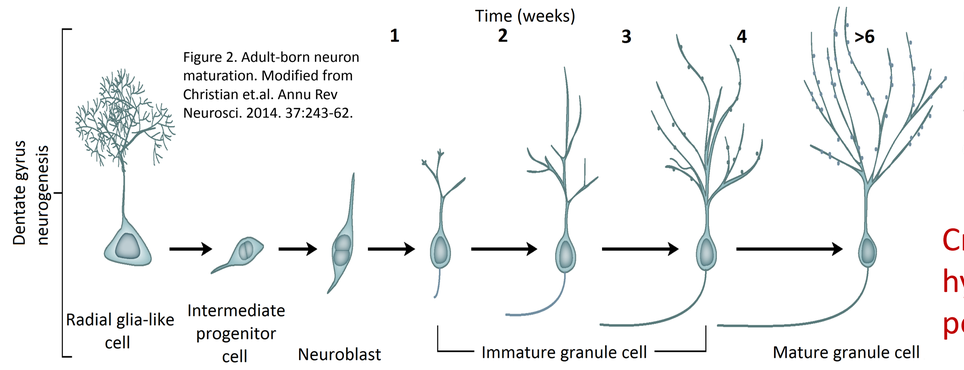


Figure 2. Adult-born neuron maturation. Modified from Christian et.al. Annu Rev Neurosci. 2014. 37:243-62.

Integration to the trisynaptic circuit

Critical hyperplastic period

Properties	Week 1	Week 2	Week 4	Mature
Afferent LTP	N/A	Weak	High	Medium
Afferent LTP threshold	N/A	Lower?	Lower	Medium
Efferent LTP	N/A	None/weak	High	Medium
Glutamate inputs	Receptors expressed	First dendritic spines	Synaptically connected	Synaptically connected
GABA inhibition	Tonic excitatory	Negligible	Negligible	Substantial
Resting membrane pot.	-40mV	-50mV	-70mV	-80mV
Input resistance	>2GΩ	2GΩ	0.5GΩ	0.3GΩ

Table 1. Properties of dentate gyrus granule cells at different times during maturation. LTP, long-term potentiation; N/A, not applicable; pot, potential.

4. Role in pattern separation

Pattern separation: transformation of similar inputs into more discordant outputs.
Representation of similar spaces or contexts as different memories.

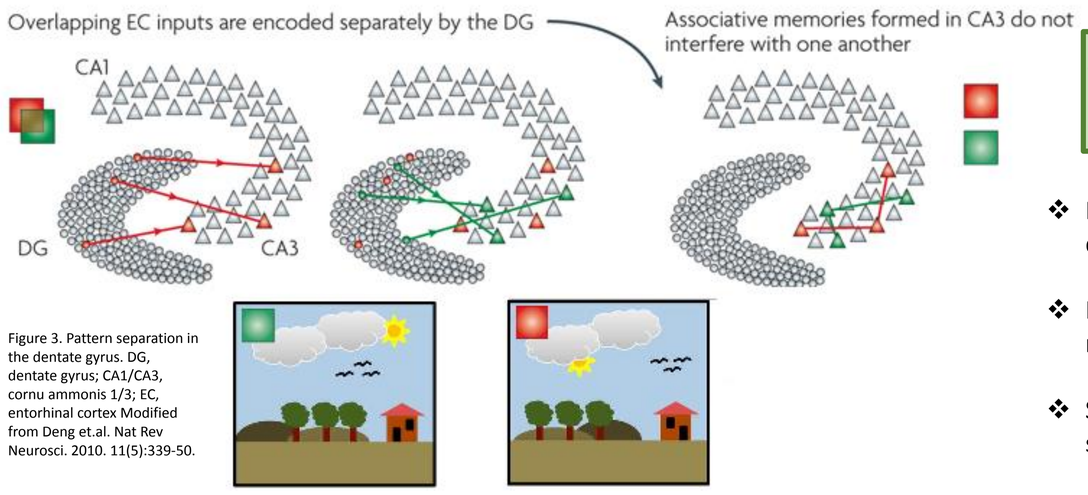
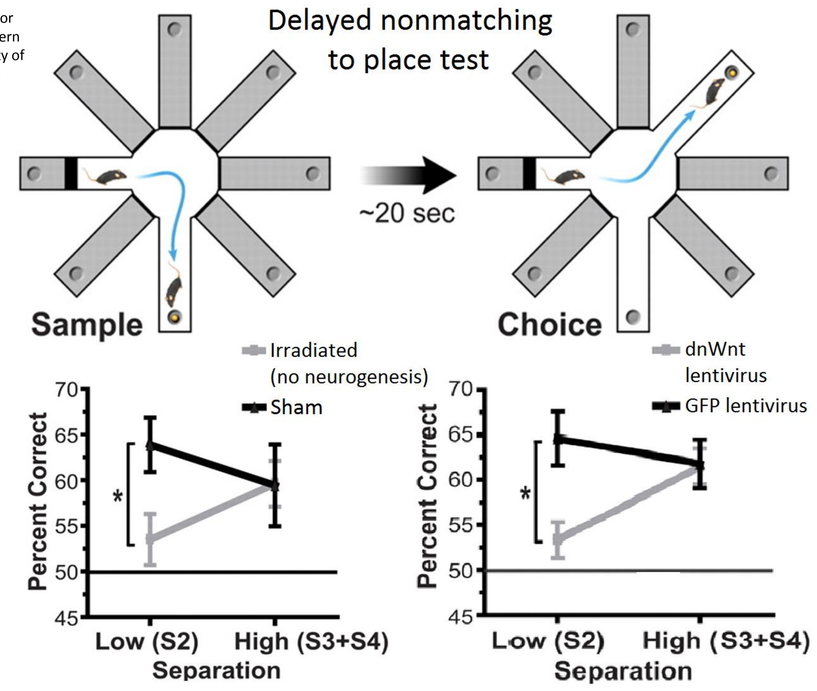


Figure 3. Pattern separation in the dentate gyrus. DG, dentate gyrus; CA1/CA3, cornu ammonis 1/3; EC, entorhinal cortex Modified from Deng et.al. Nat Rev Neurosci. 2010. 11(5):339-50.

Figure 4. Adult neurogenesis ablation using x-ray irradiation or dominant negative Wnt (dnWnt) lentiviral injection and pattern separation testing in a radial arm maze. Separation: proximity of the two open arms in choice phase. *p<0.05. Modified from Clelland et.al. Science. 2009. 325(5937):210-3.

Adult neurogenesis manipulation studies
↑neurogenesis = ↑pattern separation
↓neurogenesis = ↓pattern separation

- ❖ Neurogenesis needed for similar, not for dissimilar, context/space discrimination
- ❖ Learning directed to new neurons: interference reduced
- ❖ Senile humans: neurogenesis and pattern separation decrease (fMRI studies)



5.Role in memory acquisition and retrieval

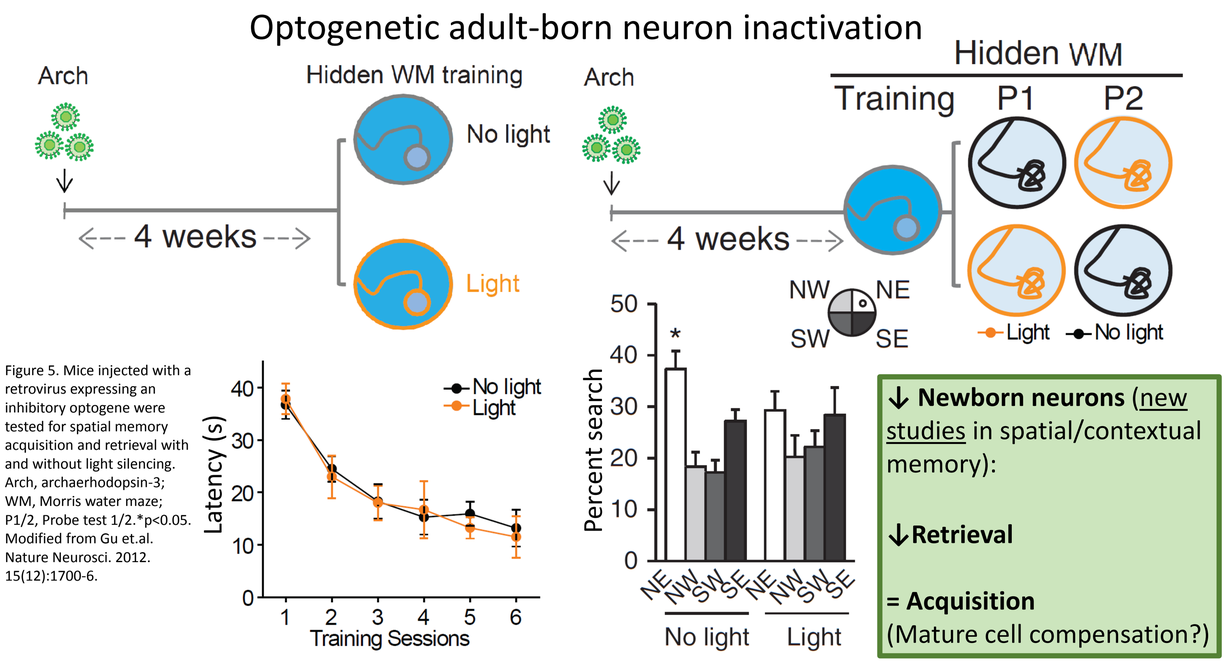


Figure 5. Mice injected with a retrovirus expressing an inhibitory optogene were tested for spatial memory acquisition and retrieval with and without light silencing. Arch, archaerhodopsin-3; WM, Morris water maze; P1/2, Probe test 1/2.*p<0.05. Modified from Gu et.al. Nature Neurosci. 2012. 15(12):1700-6.

↓ **Newborn neurons** (new studies in spatial/contextual memory):

↓Retrieval

= Acquisition
(Mature cell compensation?)

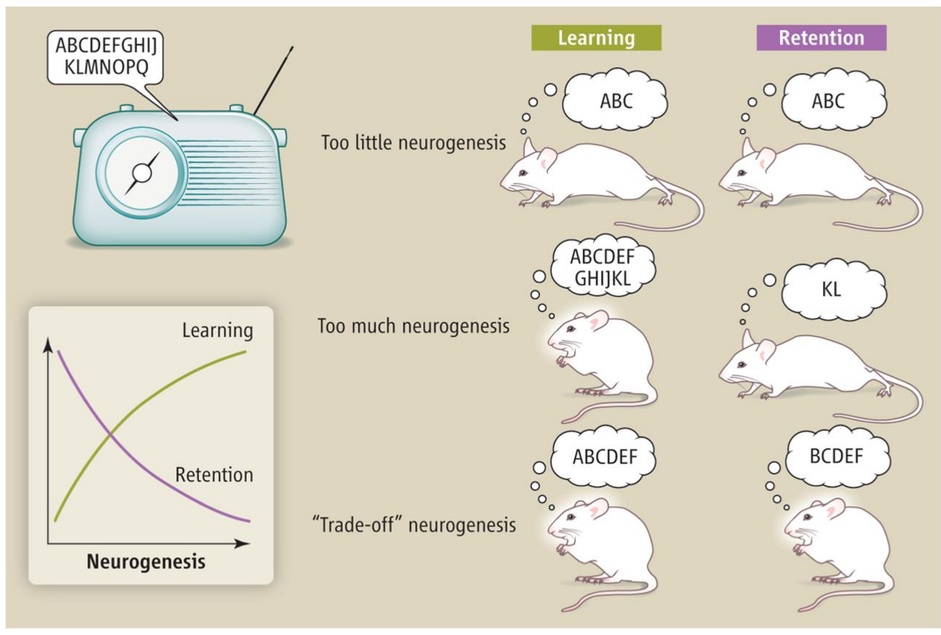
❖ Old ablation studies:
↓Neurogenesis
(contextual/spatial memory)

↓Acquisition
↓Retrieval

Inconsistent results

- Strain variability
- Technique variability
- Technique unspecificity

6. Role in memory forgetting



↑Neurogenesis posttraining

↓Retrieval

- ❖ Axons of new neurons destabilize preexisting synapses
- ❖ Potential role in systems memory consolidation

Figure 6. Theory for adult neurogenesis effect over learning and memory retention. From Mongiat et.al. Science. 2014. 344(6184):594-5.

7. Human adult neurogenesis

- ❖ Comparable neurogenesis rate
- ❖ Increased turning over population
- ❖ Longer maturation period (≥6 months)
- ❖ Reduced neurogenesis age decline
- ❖ Neurogenesis alterations in disease
  - Alzheimer, Fragile X, epilepsy

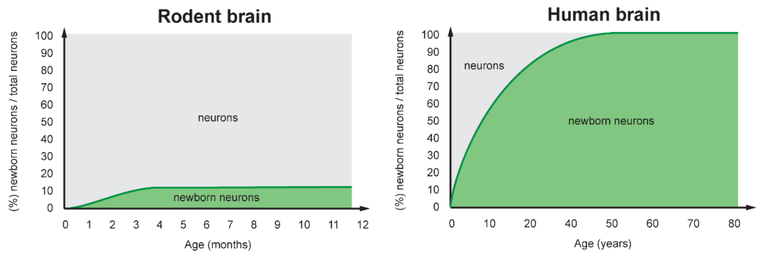


Figure 7. Adult neurogenesis cell turnover in the rodent and human brain. Modified from Ernst et.al. PLoS Biol. 2015. 13(1):e1002045.

8. Conclusions

1. Immature adult-born neurons show different properties from mature neurons during a critical period, being more plastic and excitable and constituting a preferential target for new learning.
2. Adult-born neurons mediate pattern separation of similar, but not dissimilar, contexts and spaces.
3. Adult-born neurons encode spatial and contextual memories participating in their retrieval, but they are not essential for their acquisition.
4. Adult neurogenesis destabilizes previously stored hippocampal memories, which could contribute to systems memory consolidation.
5. Humans present differences in adult neurogenesis compared to rodents representing a possible difference in functional significance.