New Neurons in Adult Brains

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Brain circle 2014

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a dogma:

Brain cells in adult animals do not renew!
Challenging the dogma (1)

[\(^3\)H] thymidine
Altman & Das
J Comp Neurol (1965)

[\(^3\)H] thymidine
Goldman & Nottebohm
PNAS (1983)

BrdU
Miller & Nowakowski
Brain Res (1988)

Fig. 3. High-power photomicrograph of a gold-thymidine-labeled anterograde and retrograde autoradiograph revealing labeled fibers in the stratum radiatum of the dentate gyrus. The animals were injected with tritiated thymidine at 2 days of age and survived for 28 days after the injection. (x400)
Challenging the dogma (2)

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- J Comp Neurol (1965)

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- Goldman & Nottebohm
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Challenging the dogma (3)

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Challenging the dogma

# of citations per year


Year

[^3H] thymidine

*Altman & Das*

*J Comp Neurol (1965)*

[^3H] thymidine

*Goldman & Nottebohm*

*PNAS (1983)*

BrdU

*Miller & Nowakowski*

*Brain Res (1988)*

I join HU

+ Olfactory bulb
Adult neurogenesis
Olfactory bulb + hippocampus
Neurogenesis in the Neocortex of Adult Primates

Elizabeth Gould,* Alison J. Reeves, Michael S. A. Graziano, Charles G. Gross

In primates, prefrontal, inferior temporal, and posterior parietal cortex are important for cognitive function. It is shown that in adult macaques, new neurons are added to these three neocortical association areas, but not to a primary sensory area (striate cortex). The new neurons appeared to originate in the subventricular zone and to migrate through the white matter to the neocortex, where they extended axons. These new neurons, which are continually added in adulthood, may play a role in the functions of association neocortex.
THE PROBLEM WAS TECHNICAL...

Do neurons regenerate into the primate’s cortex?

From: Kornack and Rakic. Science (2001)
Adult neurogenesis anywhere else?

NO!
(at least not in significant big numbers…)
How do they develop? Why do they develop in OB and Hippocampus? Are they functional?

What is the secret of these cells?

The literature claimed they are extremely important in young age, allowing plasticity to occur…
Adult neurogenesis in the olfactory system

**Target**
(olfactory bulb)

**Source**
(stem cell niche)
OLFACTION – THE SENSE OF SMELL
Olfaction is potent
Olfaction is potent

Mother rabbit nurtures her pups ONLY 4-5 min once a day during the first 2 weeks after birth (0.35% of her time !)

Methylbut-2-enal-2 -
A rabbit odor released by the mother and detected by the pup.

Schaal et al. 2003 Nature
Pup retrieval behavior – in the lab

Mother (P3)

Naïve virgin

Animals retrieving pups, %

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<th>60</th>
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<td>Naïve</td>
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<td>Mothers</td>
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<td>Mothers (wash pups)</td>
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Time to retrieve, s

- Mothers
- Mothers- Washed pups

Pup

1st 2nd 3rd 4th 5th
The olfactory bulb
Watching neurons in the making, *in vivo*

An image can convey a thousand words

Video even more
Watching neurons in the making, \textit{in vivo}

\textit{How do we see the invisible?}

- **IMAGING**
  - Target (olfactory bulb)

- **VIRUSES**
  - Stem cell niche

Mizrahi, Nature Neurosci. 2007
Seeing the invisible

1. Viruses (genetics)
Seeing the invisible

2. Two-Photon microscopy

Two photon excitation is limited to the focal plane
Seeing the invisible

*Combining genetics (viruses) and imaging*

"Regular" microscopy
(fishing)

Two-photon microscopy
(scuba diving)
Watching neurons in the making, *in vivo*

(10 days) → (12 days) → (1 month) → (3-9 months)

**IMAGING**
Target (olfactory bulb)

**VIRUSES -GFP**
Stem cell niche

Mizrahi, Nature Neurosci. 2007
Adult Neurogenesis – LIVE!
Average intensity projection (9 sessions)

Young newborn neurons are like Israel's

First “LISTEN”

Then “TALK”

Synaptic outputs (Synaptophysin-GFP)

Synaptic inputs (PSD95-GFP)

Experience upregulates adult neurogenesis.

SEX... SCANDAL... CELEBRITY...
SOME THINGS NEVER CHANGE.

A FILM BY
STEPHEN FRY

BRIGHT YOUNG THINGS

EMILY MORTIMER, STEPHEN CAMPBELL MOORE, DAN ACKROYD, JIM BROADBENT, SIMON CALLOW, GUY HENRY, JAMES McAVOY, JULIA MCKENZIE, JOHN MILLS, ALEC NEWMAN, BILL PATERSO, MICHAEL SHEEN, IMELDA STAUNTON, DAVID TENNANT, HARRIET WALTER, FENELA WOOLGAR, AND PETER O'TOOLE

THE FILM CONSORTIUM PRESENTS IN ASSOCIATION WITH UK FILM COUNCIL AND VEROMAR, IN CO-PRODUCTION WITH REVOLUTION FILMS, FOCUS FILMS AND XON FILM DISTRIBUTION. PRODUCED BY TREVOR WADDELL AND ROB BONNER. WRITTEN AND DIRECTED BY STEPHEN FRY. EXECUTIVE PRODUCERS ARE ROBERT HADDEN, MICHAEL ATHERTON, AND GARY CANT. PRODUCTION MANAGER IS PETER J. MONTGOMERY. DIRECTOR OF PHOTOGRAPHY IS TONY HEITZ. EDITOR IS PETER MAYHEW. MUSIC COMPOSED AND PERFORMED BY PAUL RICHARDS. ASSISTANT DIRECTOR IS MARK SHERWOOD. FIRST ASSISTANT PRODUCER IS TIGGY JACOBSON. SET DEPARTMENTS ARE MARK JONES AND ELAINE KEMP. COSTUME DESIGN IS MARY HENSON. MAKE-UP AND HAIR DESIGN IS SARAH WADDELL. CAST INCLUDES STEPHEN CAMPBELL MOORE, ROBERT HADDEN, JOHN MILLS, ALEC NEWMAN, BILL PATERSO, MICHAEL SHEEN, IMELDA STAUNTON, HARRIET WALTER, AND PETER O'TOOLE.

FEATURING MAX FACTOR, THE MAKEUP OF THE MOVIE.
Do fully mature adult-born neurons also show experience dependent plasticity?
Experience STABILIZES adult born neuron dynamics
Do they even respond to sensory stimuli?
Are they different from “resident” neurons?
Do they contributing to coding? If so, when?
Yes - Adult-born neurons become fully functional!
Adult-born neurons are initially promiscuous

Livneh et al. Neuron (2014)
Adult-born neurons are sensitive to experience and become “specialized” when challenged.

What next?
Experience dependent plasticity

Well controlled lab conditions

Motherhood

Wild

RFID Ant
IR beam

Perceptual learning
Pregnancy-Stimulated Neurogenesis in the Adult Female Forebrain Mediated by Prolactin

Tetsuro Shingo,* Christopher Gregg, Emeka Enwere, Hirokazu Fujikawa, Rozina Hassam, Colleen Geary, James C. Cross, Samuel Weiss†

Neurogenesis occurs in the olfactory system of the adult brain throughout life, in both invertebrates and vertebrates, but its physiological regulation is not understood. We show that the production of neuronal progenitors is stimulated in the forebrain subventricular zone of female mice during pregnancy and that this effect is mediated by the hormone prolactin. The progenitors then migrate to produce new olfactory interneurons, a process likely to be important for maternal behavior, because olfactory discrimination is critical for recognition and rearing of offspring. Neurogenesis occurs even in females that mate with sterile males. These findings imply that forebrain olfactory neurogenesis may contribute to adaptive behaviors in mating and pregnancy.

Shingo et al. Science, 299, 11

Sakamoto M et al. PNAS
Thy1-GCamp3 mouse, in vivo

Z-stack

Single optical plane (-280)

Yael Shlomai, unpublished
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Yoav Livneh

Yael Shlomai

Israel Science Foundation

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