



UNIVERSITY OF GOTHENBURG

Experimental approaches to CNS late effects

Klas Blomgren

Department of Pediatric Oncology
The Queen Silvia Children's Hospital
and

Center for Brain Repair and Rehabilitation
Institute of Neuroscience and Physiology

The Sahlgrenska Academy

Late effects

Radiotherapy-related effects on cognition:

- Memory – difficulties to learn new things
- Attention deficits
- Reduced stamina and patience
- More pronounced side effects in younger children

- Why?

Platforms, models

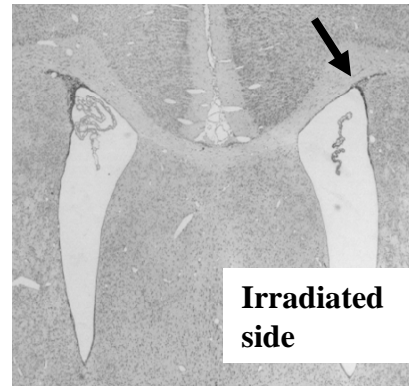
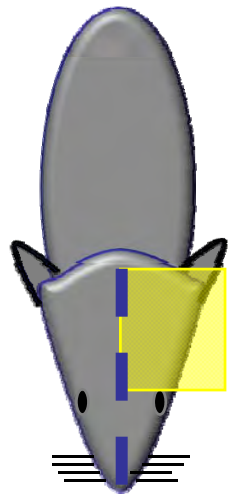
- Irradiation - *in vivo* and *in vitro*
- Cell grafting
- Cell death
- Behavior / functional assessment

Platforms, models

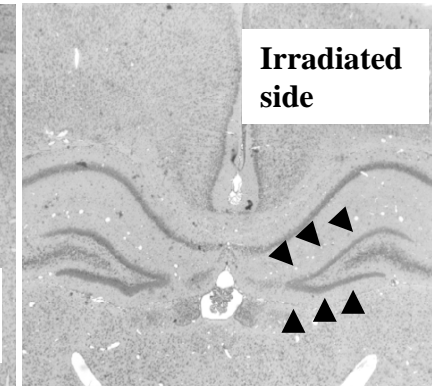
- **Irradiation - *in vivo* and *in vitro***
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Irradiation – *in vivo*

Two areas always injured by irradiation



The subventricular zone



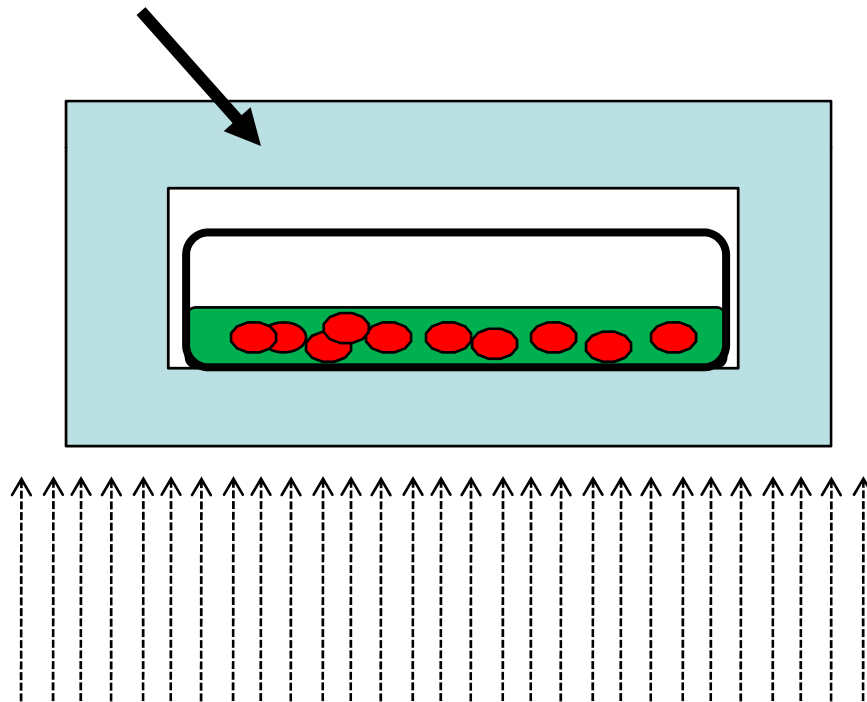
The hippocampus (dentate gyrus)

Stem cells and progenitors – proliferating cells

Fukuda 2004 *Cell Death Differ*

Irradiation – *in vitro*

Plastic box to obtain even side scatter in the medium



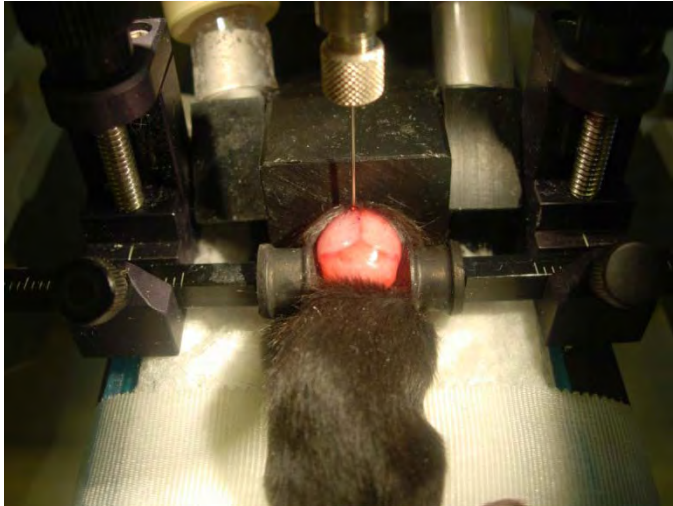
4 MV photons

- Cell lines
- Rodent neurospheres
- Human neurospheres

Platforms, models

- Irradiation - in vivo and in vitro
- **Cell grafting**
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Cell grafting



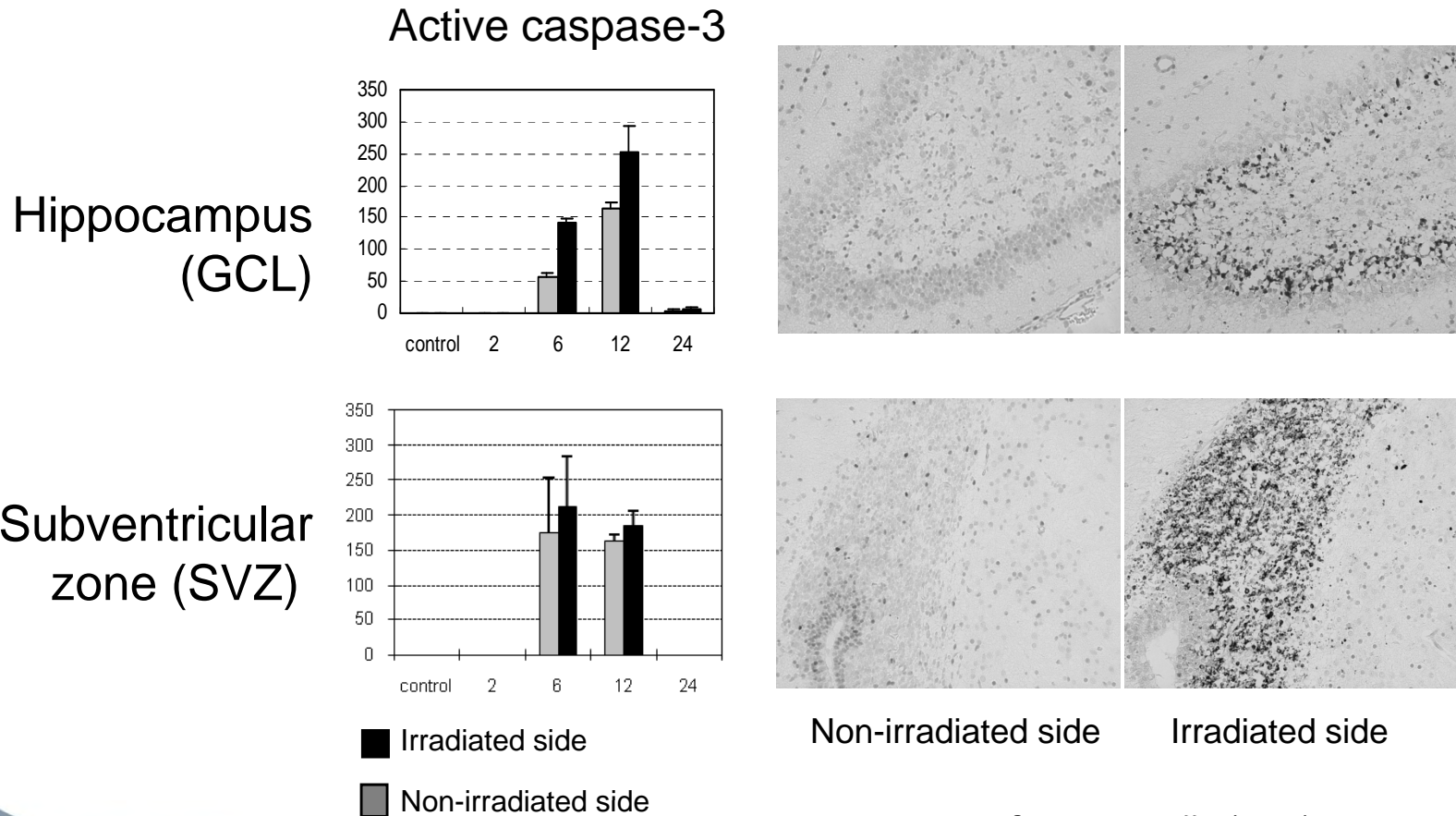
- **Neural precursor cells (syngeneic)**
- **Glioblastoma cells (GFP labeled, syngeneic)**

Platforms, models

- Irradiation - in vivo and in vitro
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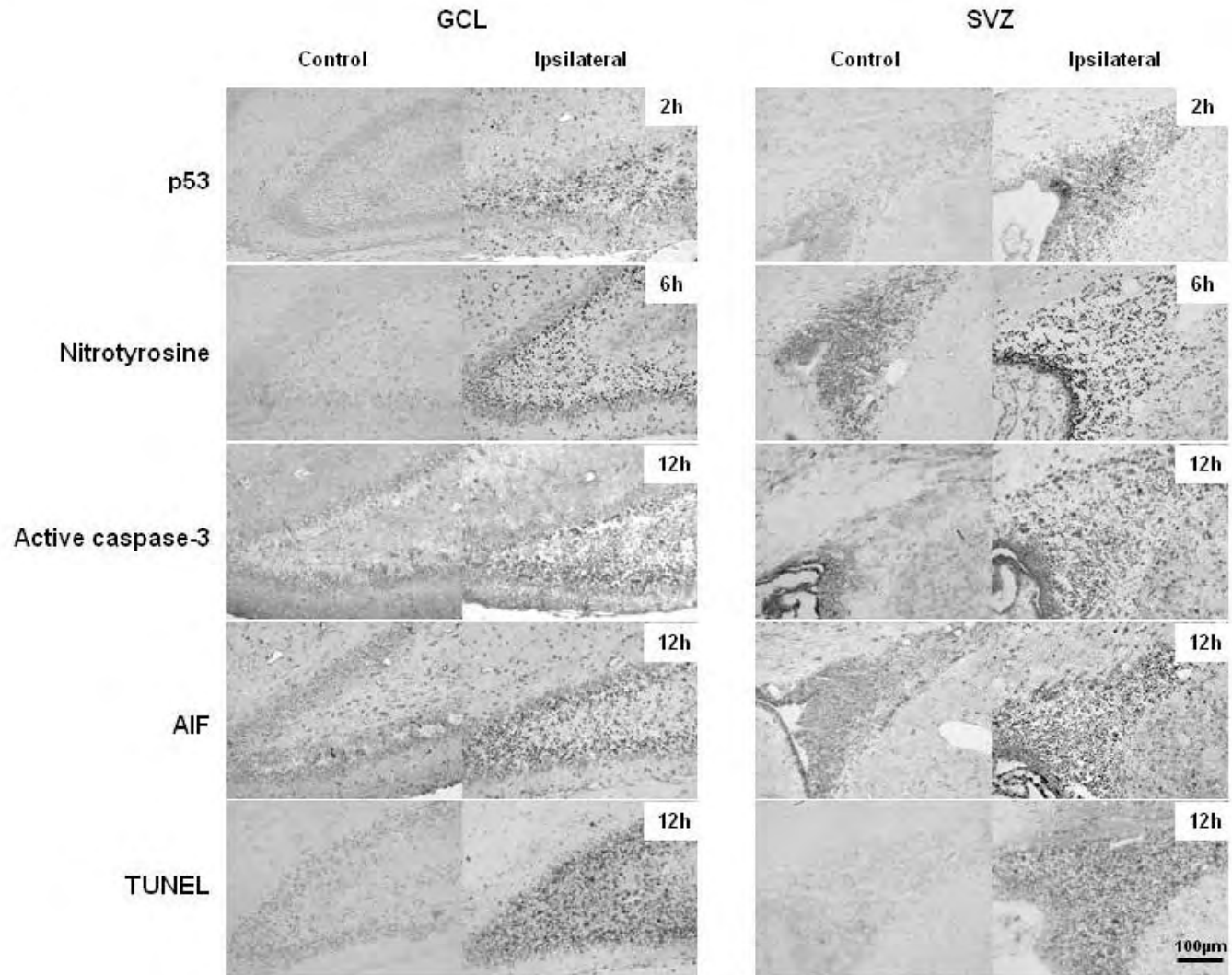
Irradiation and cell death

Stem cells and progenitors die within hours



Fukuda et al. *Cell Death Differ* (2004) 11:1166-78

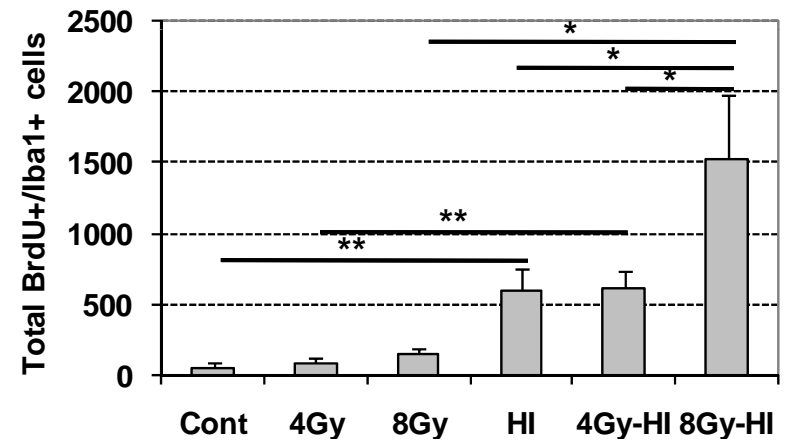
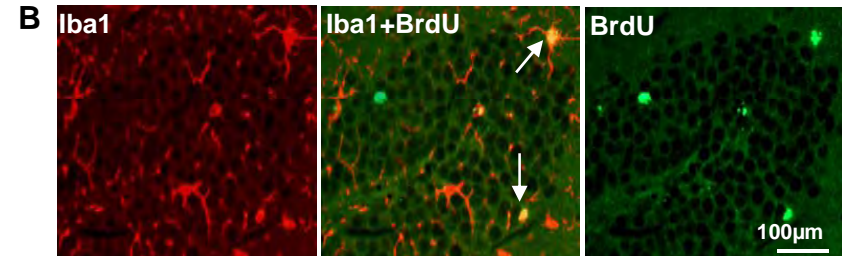
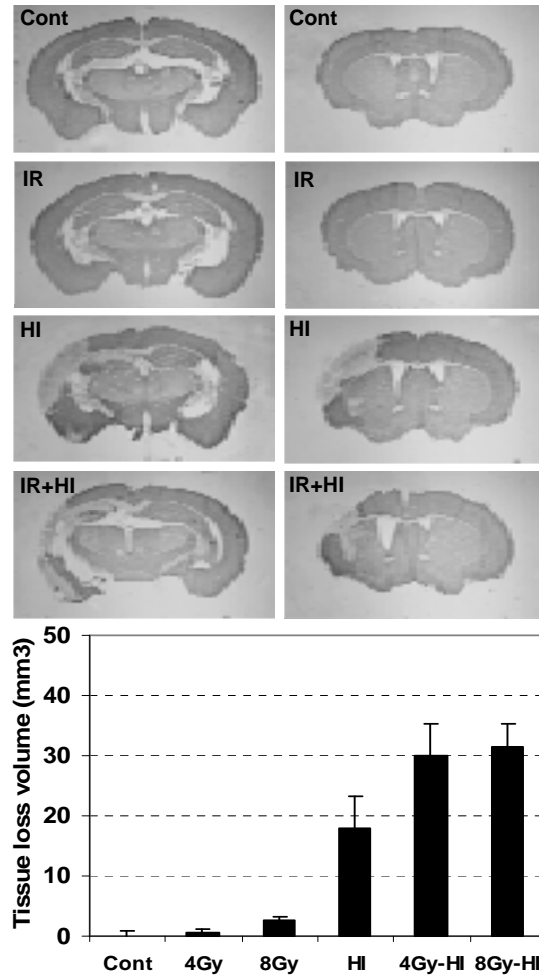
Irradiation and cell death



Cell death

- Regulation of caspase activation
(Blomgren 2001 JBC, Zhu 2007 CDD)
- Regulation of AIF
(Zhu 2007 J Exp Med, Zhu 2007 CDD)
- Autophagy and p53
(Tasdemir 2008 Nat Cell Biol)
- Oxidative stress
(Zhu 2005, 2007 CDD)

IR of young mice followed by ischemia in adulthood



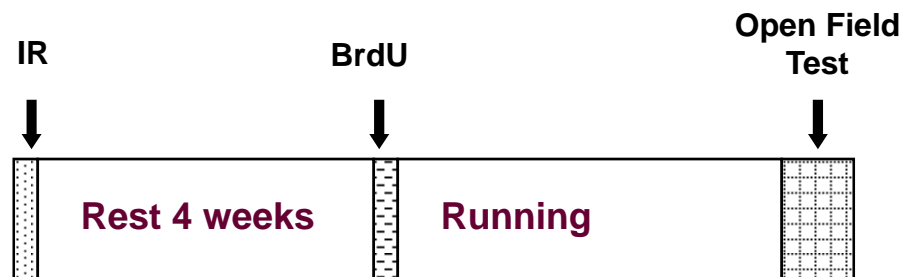
The increased injury can only partly be explained by direct damage to neurogenic regions

Platforms, models

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- **Behavior / functional assessment**

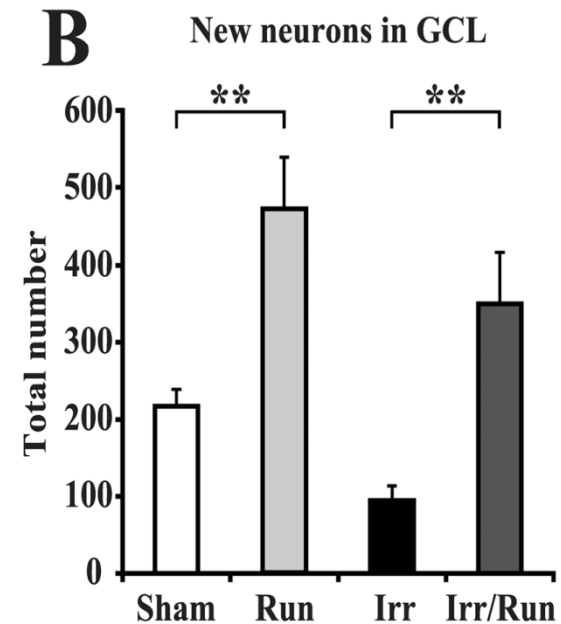
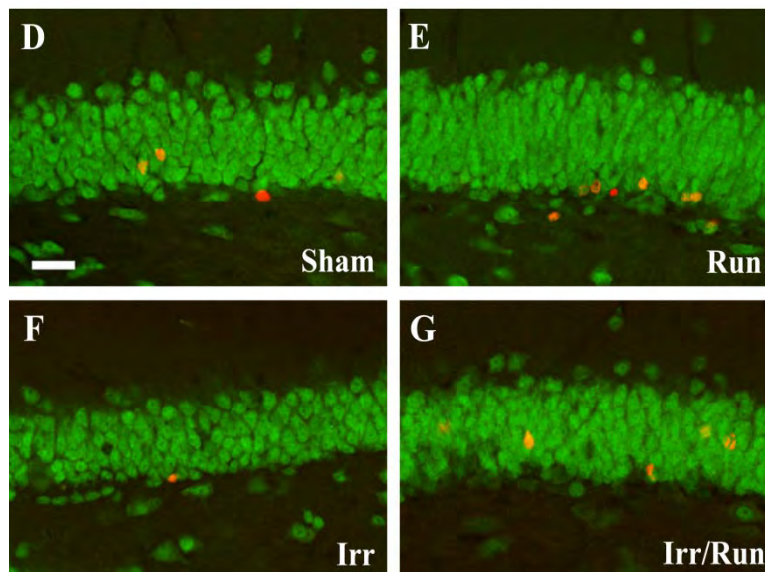
Behavior, functional assessment

Voluntary running after IR



Behavior, functional assessment

Voluntary running after IR



**Neurogenesis decreased after IR
and increased several-fold after running**

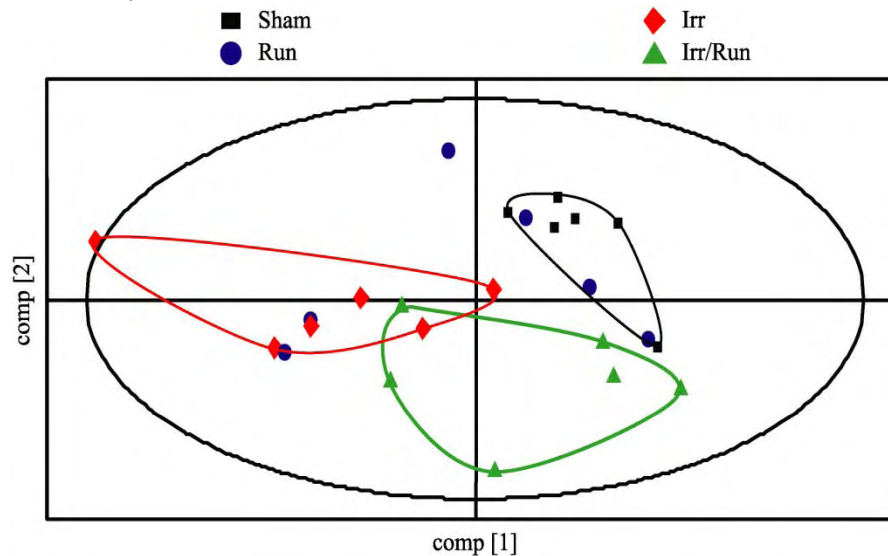
Naylor 2008 PNAS

Behavior, functional assessment

Voluntary running after IR

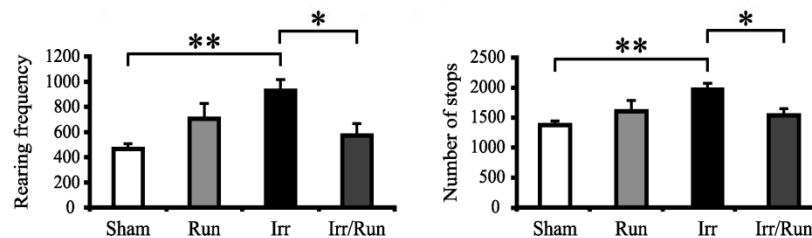
Multivariate evaluation of behaviour

PLS-DA, Score Plot



Open field test:

IR caused hyperactive behavior and this was partly normalized by running

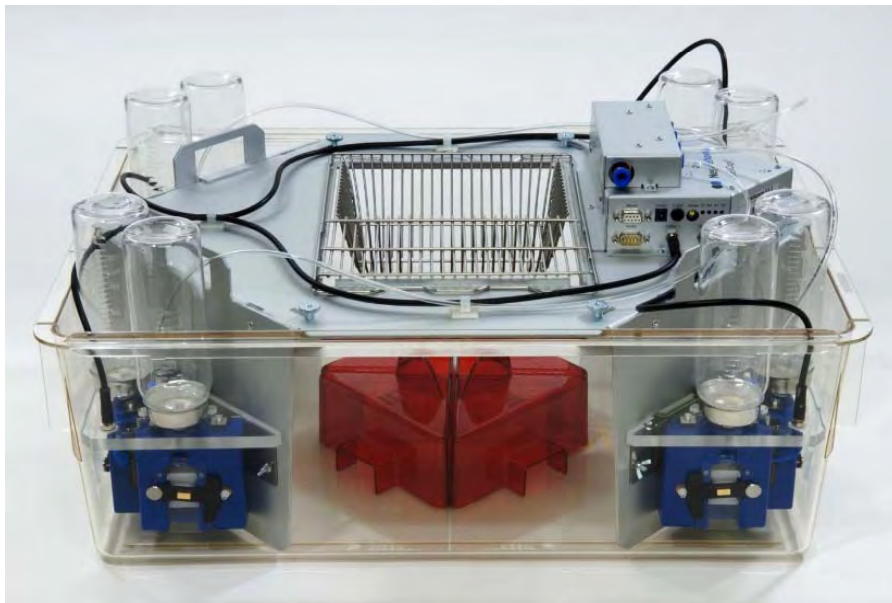


Naylor 2008 PNAS

Behavior, functional assessment

IntelliCage

(www.newbehavior.com)



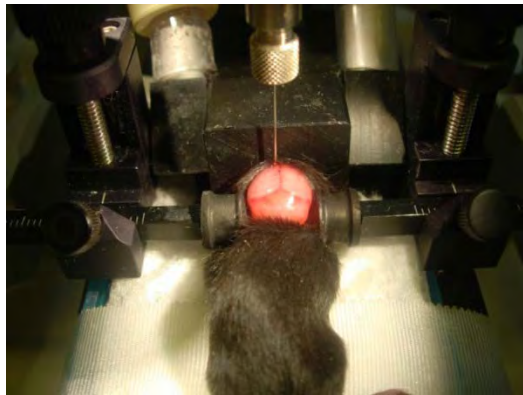
Behavior, functional assessment

IntelliCage

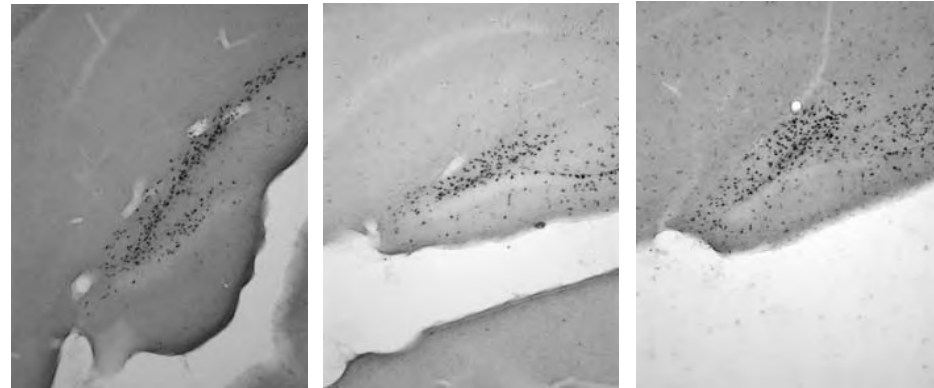


Behavior, functional assessment

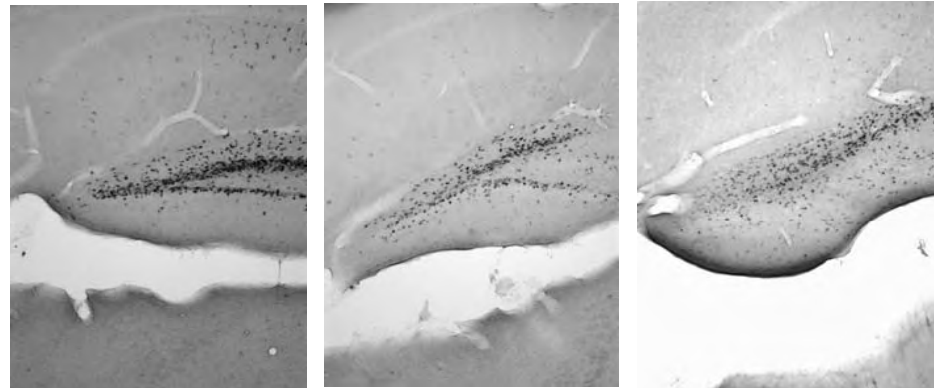
Grafting of stem cells



IR



Non-IR



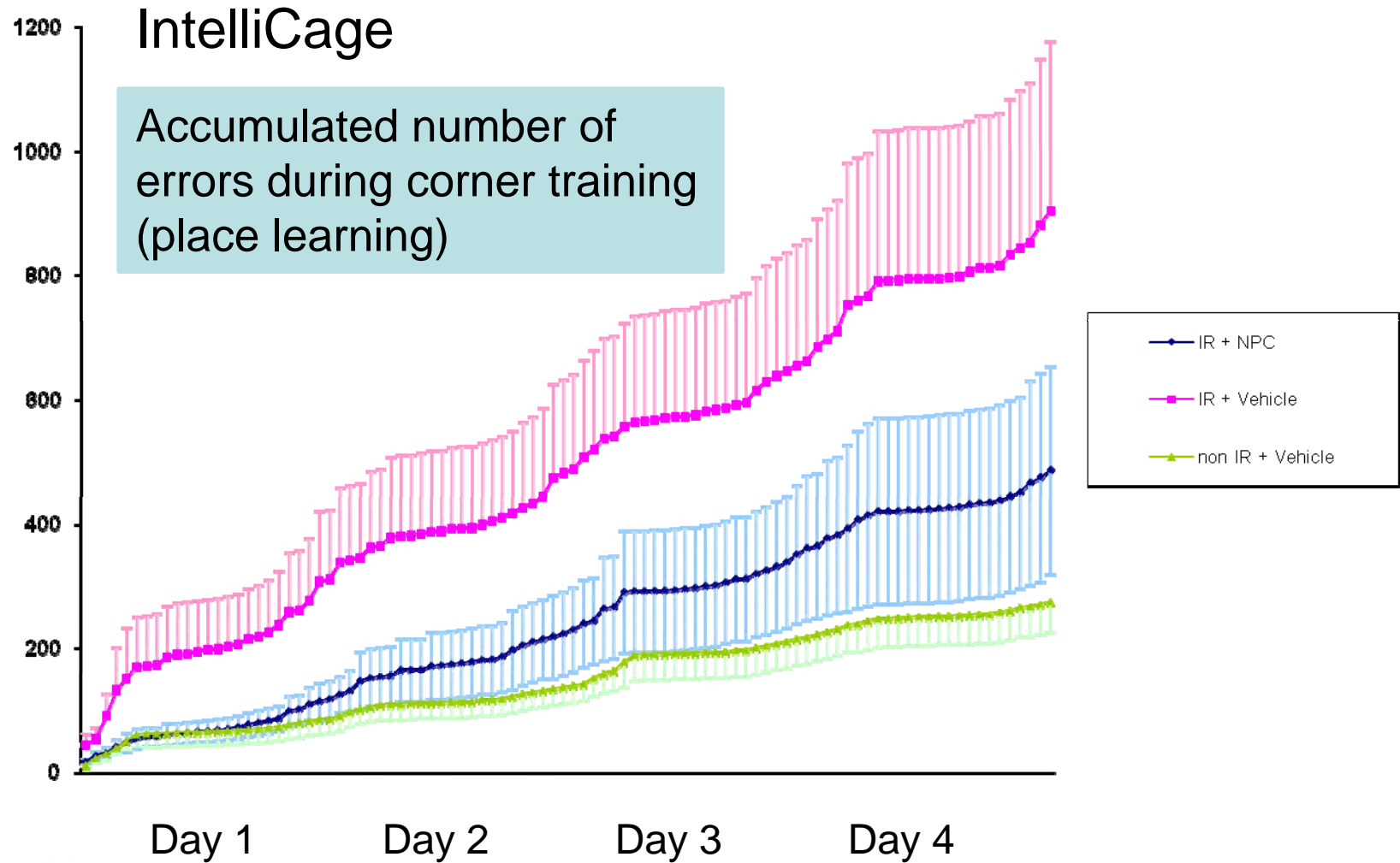
Grafting after:

1 day

1 week

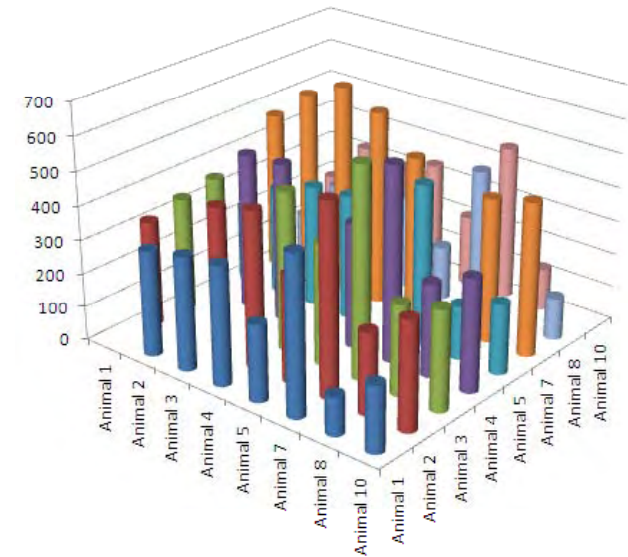
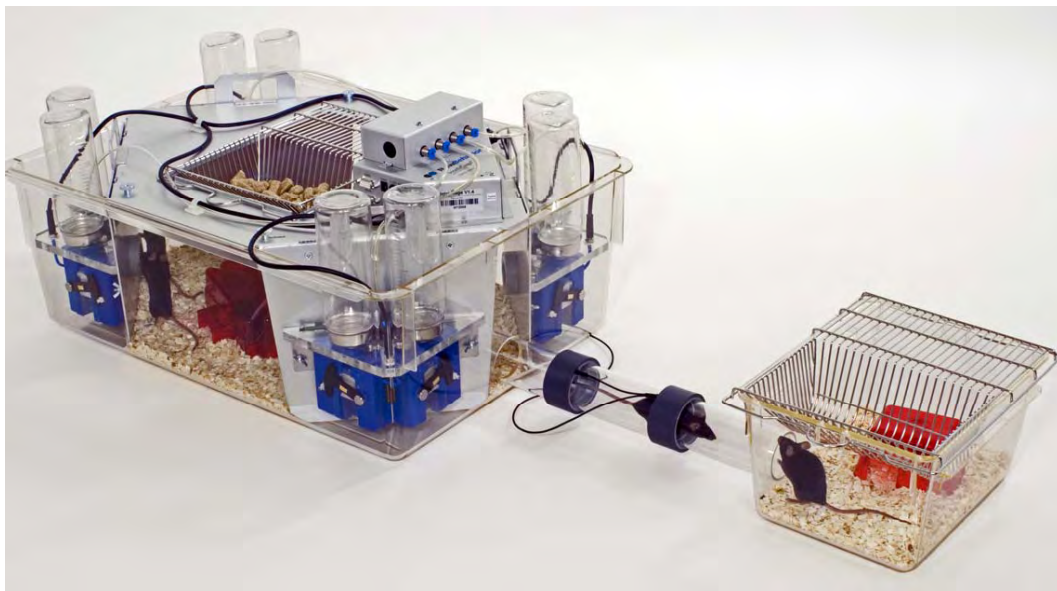
6 weeks

Behavior, functional assessment



Behavior, functional assessment

IntelliCage + Social Box



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Coworkers

Rita Grandér

Malin Johnson

Marie Kalm

Niklas Karlsson

Qian Li

Tomoyo Ochiishi

Karolina Roughton

Magnus Sabel

Yoshiaki Sato

Changlian Zhu

Georg Kuhn, *Gothenburg*

Birgitta Lannering, *Gothenburg*

Thomas Björk-Eriksson, *Copenhagen*

Milos Pekny, *Gothenburg*

Marcela Pekna, *Gothenburg*

Michael Nilsson, *Gothenburg*

Guido Kroemer, *Paris*



Vetenskapsrådet



UNIVERSITY OF GOTHENBURG