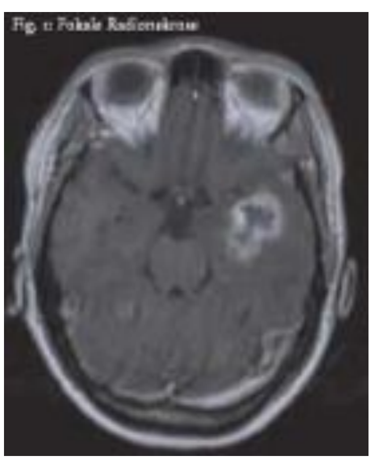
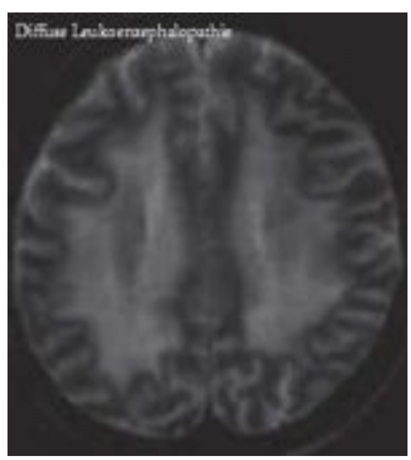
OncoRay – National Center for
Radiation Research in Oncology, Dresden

Biological bases of neurotoxicity

Nils Cordes





First description of cerebral Radionecrosis

*Fischer & Holfelder **1930** after irradiation of a basal cell carcinoma of the skin of the head*

„Lokales Amyloid im Gehirn“
*Dtsch Z Chir **1930**; 227: 475-483*

Why do we care about radiation effects in the brain?

Clinical exposure – radiotherapy works!

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- ~ 1/3 of the 1.5 million cancers diagnosed will develop brain mets (2nd most common site).

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- Brain tumors treated with radio(chemo)therapy
- ~ 1/3 of the 1.5 million cancers diagnosed will develop brain mets (2nd most common site).
- For many of these metastatic lesions along with primary tumors (~ 25,000 new cases/yr), radiotherapy remains a primary treatment modality involving ~ 200,000 patients/year that receive partial or whole brain irradiation.
- More people are living longer with serious side effects resulting from cranial irradiation.

RTOG/EORTC acute brain/CNS side effects

Grad 0	No change
Grad 1	Fully functional status (i.e., able to work) with minor neurologic findings, no medication needed
Grad 2	Neurologic findings present sufficient to require home case/nursing assistance may be required/medications including steroids/anti-seizure agents may be required
Grad 3	Neurologic findings requiring hospitalization for initial management
Grad 4	Serious neurologic impairment which includes paralysis, coma or seizures >3 per week despite medication/hospitalization required

Influences for appearance of radiogenic brain/CNS damage

Radiotherapy	Total dose Daily dose Radiation volume
Patient	Age Diabetes Hypertention Hormons
Medication	Chemotherapy (MTX, Cisplatin, 5-FU, Ara-C, Ifosfamid, ACNU, Interleukin-2, Interferon, …)

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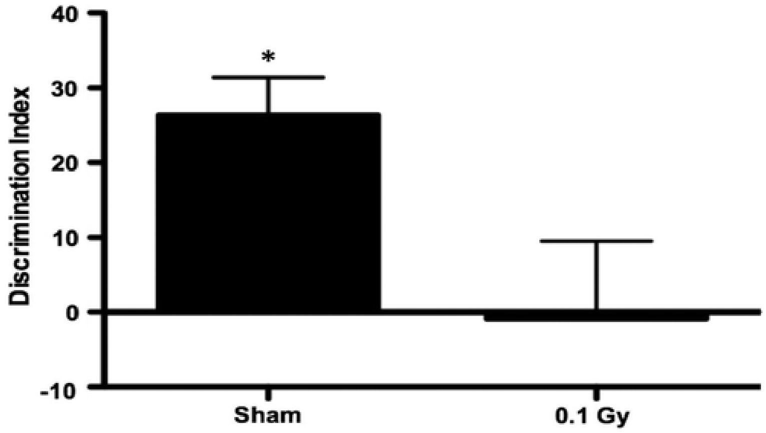
Irradiated Mice Fail to Discriminate the Novel Object

2 weeks post irradiation

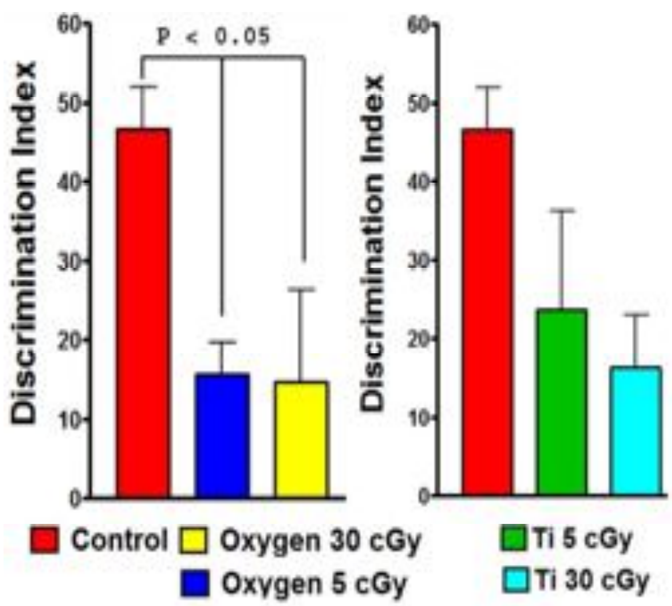


Novel object recognition of sham-irradiated and 56Fe-irradiated male mice.
The DI shows reduced exploratory preference for the novel object over the familiar object 2-weeks after irradiation with 0.1 Gy. *N*=8 mice/treatment. *$p<0.05$ (two-tailed *t*-test).

Tseng BP, Limoli CL, et al. Antioxid Redox Signal. 2014 Mar 20;20(9):1410-22.

Irradiated Mice Fail to Discriminate the Novel Object

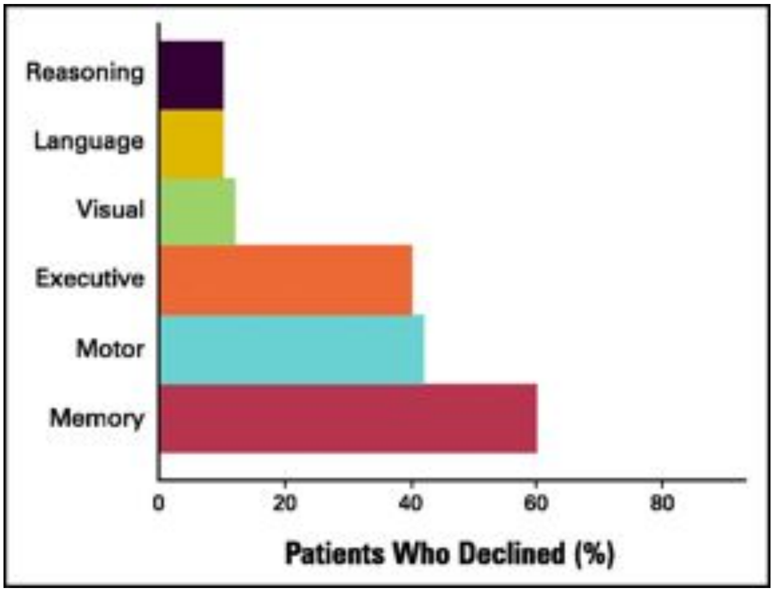
12 weeks post irradiation



= 0.05 Gy
= 0.3 Gy

Tseng BP, Limoli CL, et al. Antioxid Redox Signal. 2014 Mar 20;20(9):1410-22.

Progressive dementia in long-term brain tumor survivors



Meyers, C. A. et al. J Clin Oncol; 24:1305-1309 2006

Brain Tumors and Cognitive Deficits

- The patients surviving this serious disease are ***almost uniformly*** disabled due to severe cognitive impairments.
- With time, there is a ***continual*** deterioration of neuro-cognitive function.
- 10% of patients develop ***progressive*** dementia, 50% to 90% show deficits on sensitive tests of cognitive function.
- Patients complain of fatigue, confusion, and cognitive impairment (decreased attention and concentration, poor short term memory, and expressive language difficulty).
- These symptoms are ***frequently*** associated with distressed mood and reduced quality of life (QOL).

Schmidinger M, 2003; Imperato JP, 1990

Chronology of radiogenic damage of the brain/CNS

	Pathology	Symptomatic
Acut	Peritumoral odema	Increased intracranial pressure
Subacut	Transient Demyelinisation	Unspecific, somnolentia-syndrome, Myelon: „L´Hermitte sign“
Chronic	Damaged endothelium, Demyelinisation, cell death, predominantely in white matter, Leukencepholopathy, focal necrosis	Cognitive effects, dementia, focal neurological deficites

Radiation-induced normal tissue injury

(1) Why do people subjected to cranial radiotherapy develop progressive dementia?
(2) What happens in the brain?

Radiation-induced normal tissue injury

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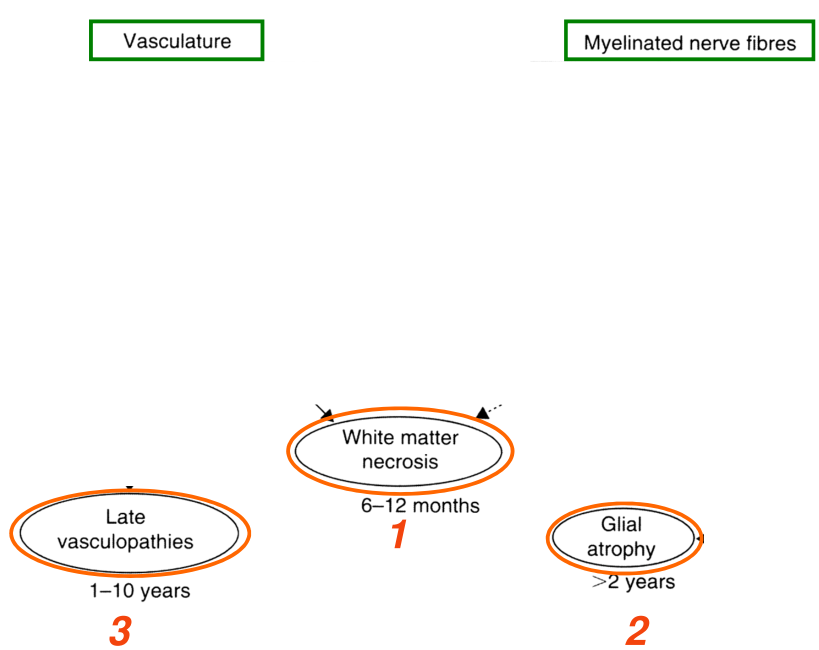
- **Acute (days) effects:**
  - Drop in the number of proliferating (Ki67 positive) precursors and immature neurons (doublecortin positivity; marker for new neurons)
- **Long-term (months) effects:**
  - Inhibition of neurogenesis
  - Cascades of secondary reactive processes involving oxidative stress and inflammation
- **Development of impaired cognition:**
  - Temporally coincident with the depletion of neural stem cells and the inhibition of neurogenesis

Sheline et al. IJROBP, 1980
Fike et al., Sem Radiat Oncol, 2009
Ngyun et al., Front Oncol, 2013
Schmidinger M, 2003; Imperato JP, 1990

Stem Cells and Neurogenesis

Pathophysiology involved in radiogenic CNS damage



Steel et al. 2002

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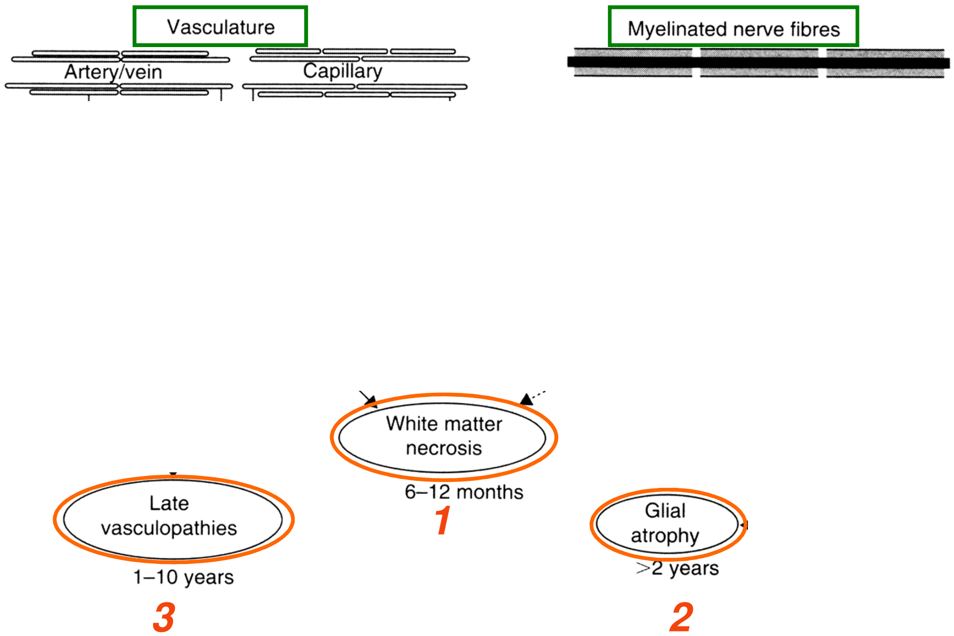

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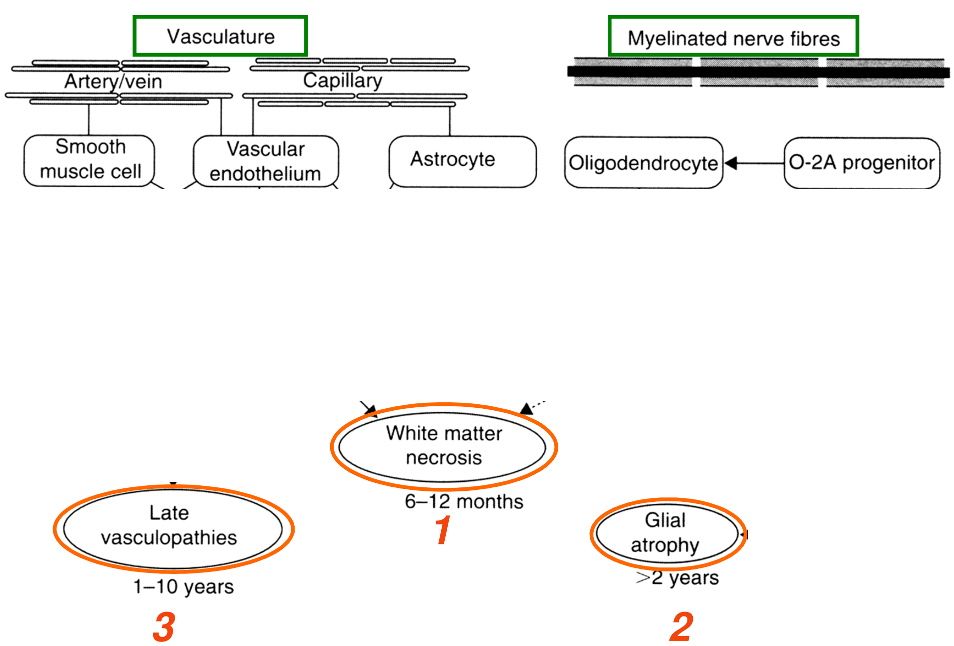

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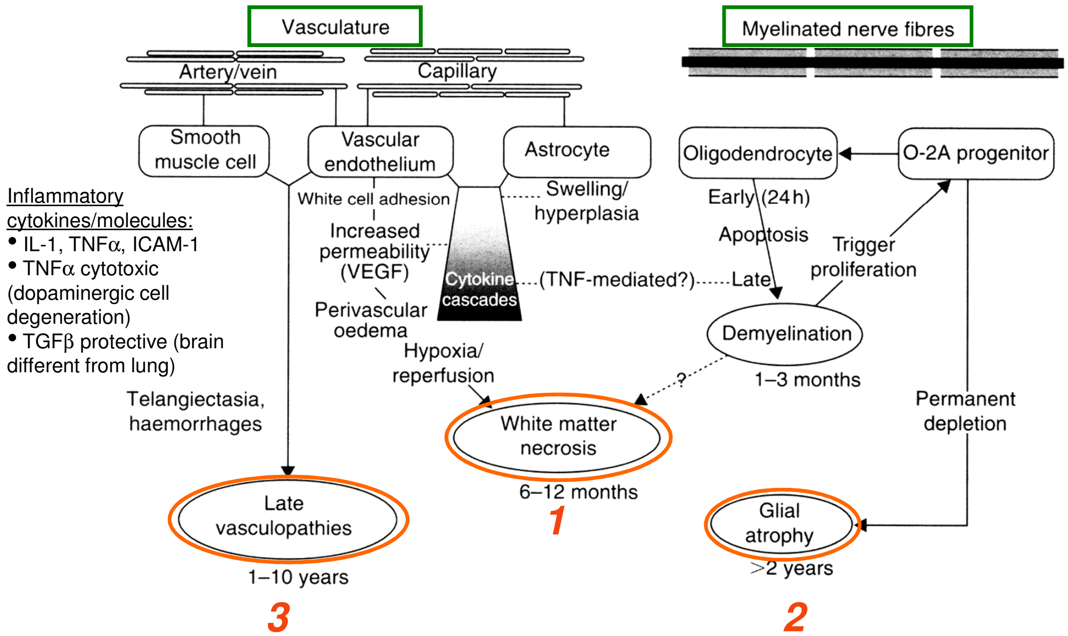

Steel et al. 2002

Molecular mechanisms - Neuronal Stem Cell therory

Table 1. Relevant characteristics of NSCs and CSCs to RT

Self-renewal
Pluripotency
High motility
Association with blood vessels
CD133+
In vitro sphere formation
Immature expression profiles
Nestin
Epidermal growth factor receptor
Hedgehog Wnt pathway
Telomerase activity

Abbreviations: CSCs = cancer stem cells; NSCs = neural stem cells; RT = radiotherapy.
Modified from data from Sanai *et al.* (27).

- *Increased rate of hippocampal apoptosis*
- *decreased rate of proliferation*
- *decrease in neurogenesis*
- *rapid ablation of the NSC compartments*

Barani et al., IJROBP 68:324-333,2007

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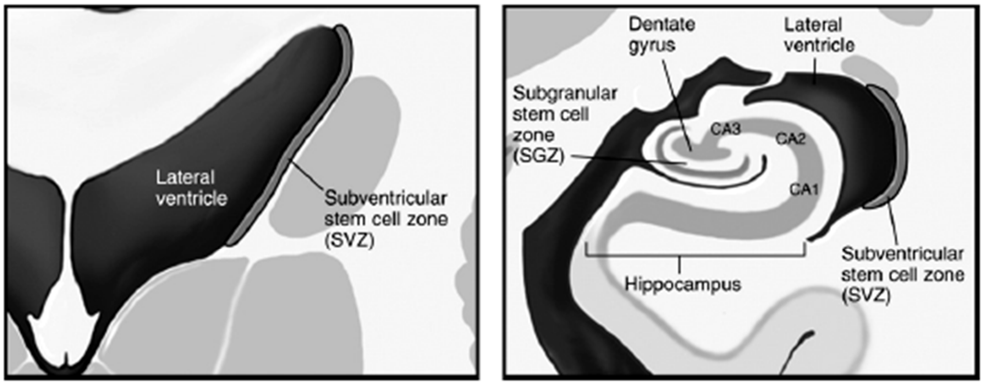
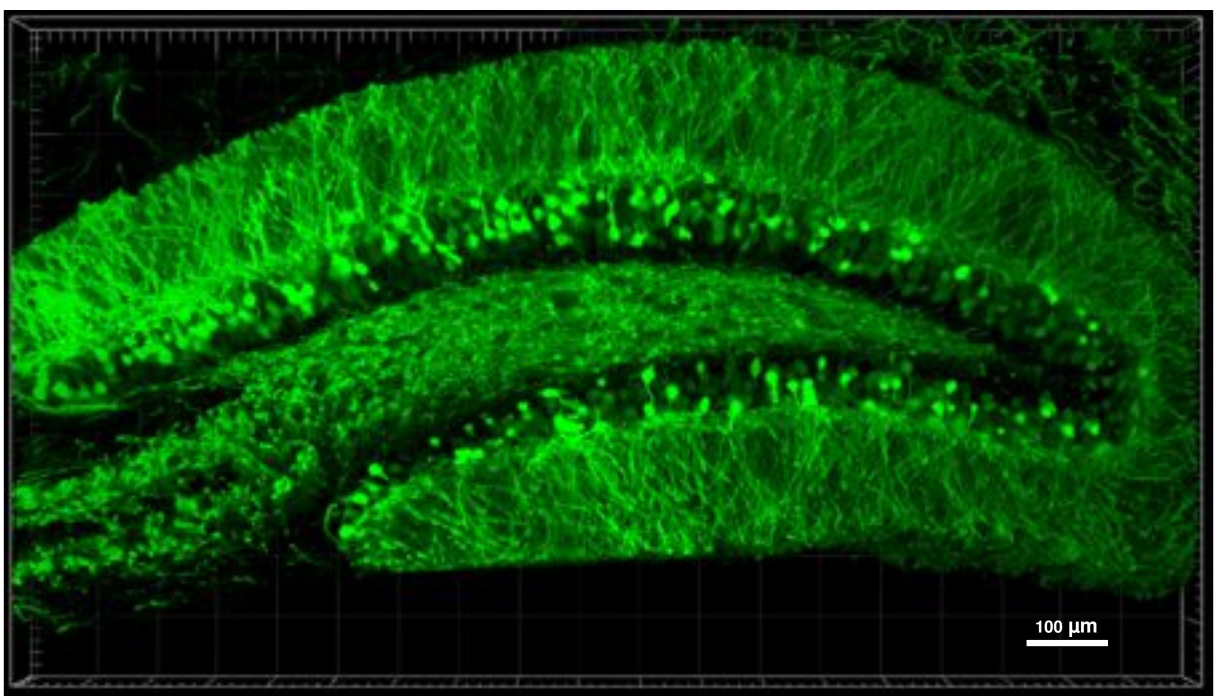


Fig. 1. Germinal regions of the adult human brain. The subventricular zone (SVZ) is the largest germinal region in the adult mammalian brain. The subgranular zone (SGZ) is located within the dentate gyrus of the hippocampus. The CA1, CA2, and CA3 represent Cornu Annulis fields of hippocampus proper and, along with dentate gyrus, constitute the hippocampal formation, the primary memory center in the brain.

Important for learning and memory –
shuttles between sensoric brain areas and cortex

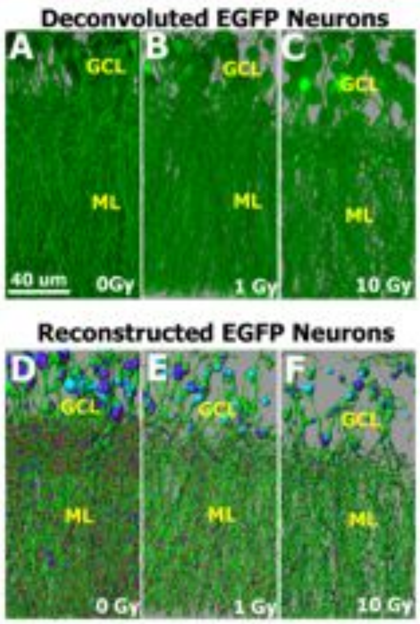
Barani et al., IJROBP 68:324-333,2007

Illuminating the hippocampus for the micromorphometric analyses of neurons following irradiation



Parihar VK1, Limoli CL. Cranial irradiation compromises neuronal architecture in the hippocampus.
Proc Natl Acad Sci U S A. 2013 Jul 30;110(31):12822-7.

Dendritic complexity is reduced 30 days following IR



GCL, granule cell layer
ML, molecular layer
(sky blue, cell body; green, dendrites; blue, branch points; red, spines)

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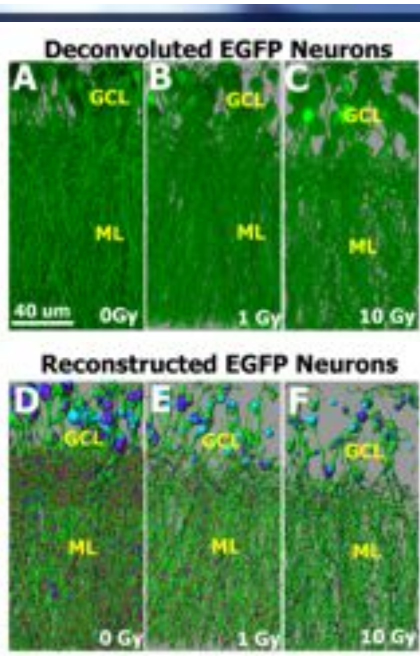

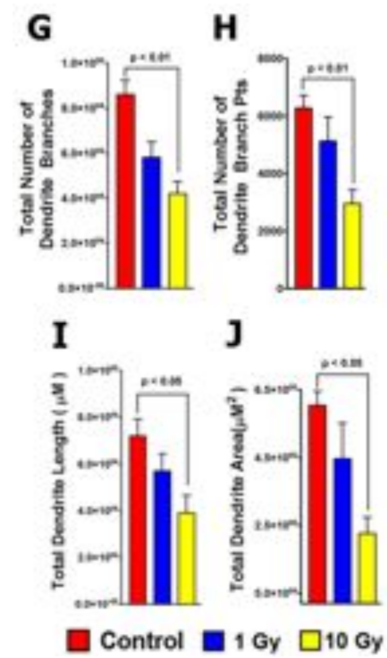

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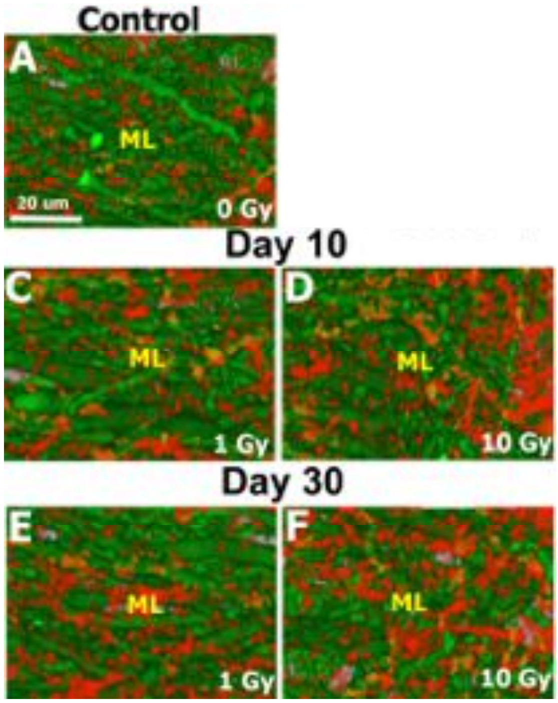
Postsynaptic density protein (PSD95) synaptic puncta after IR



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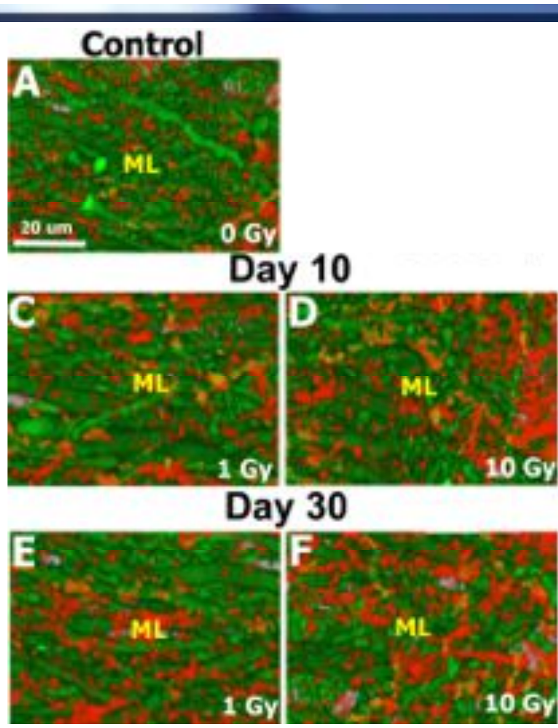

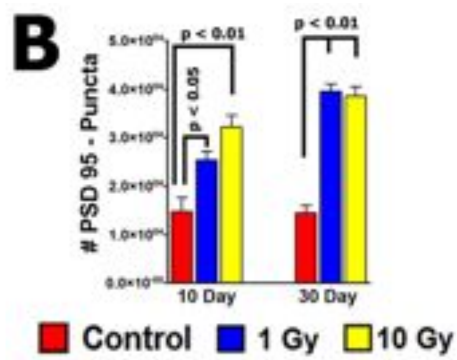

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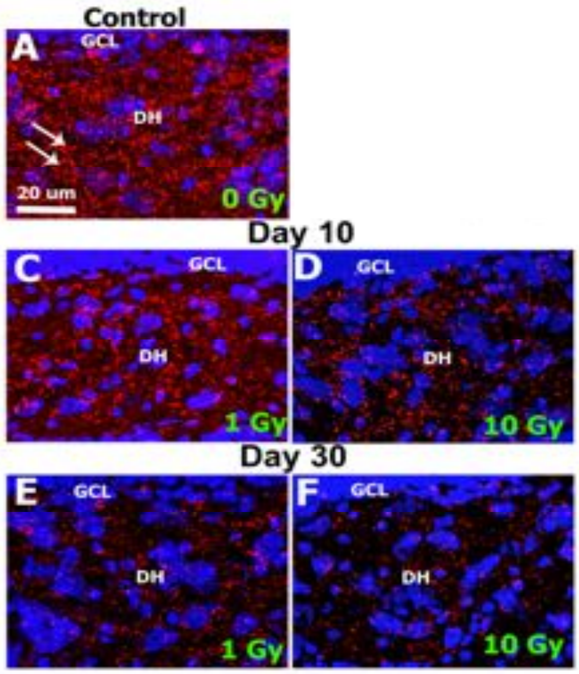

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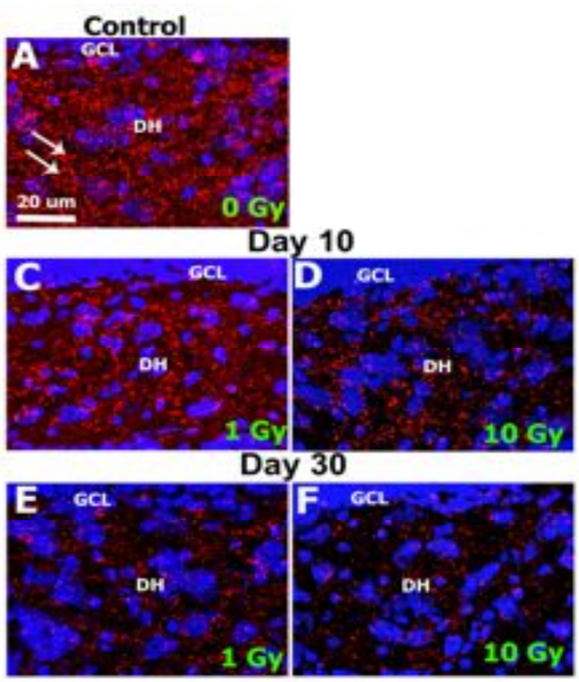

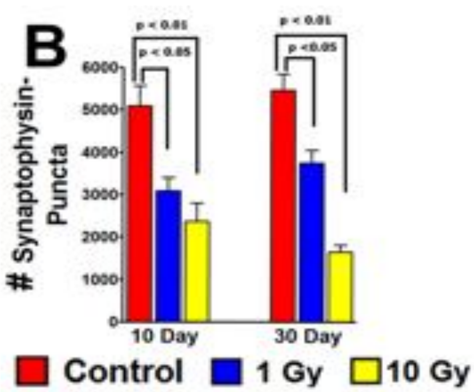

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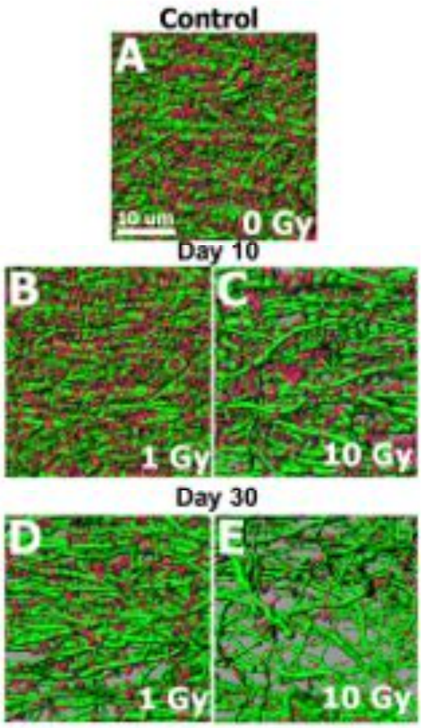
Persistent reductions in spine density and volume after IR



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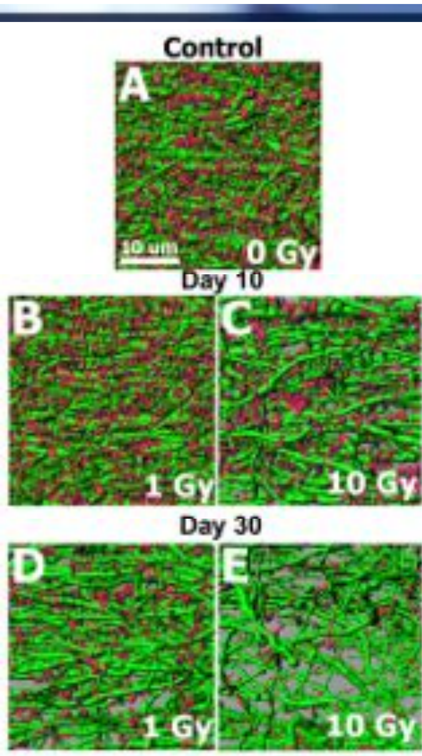

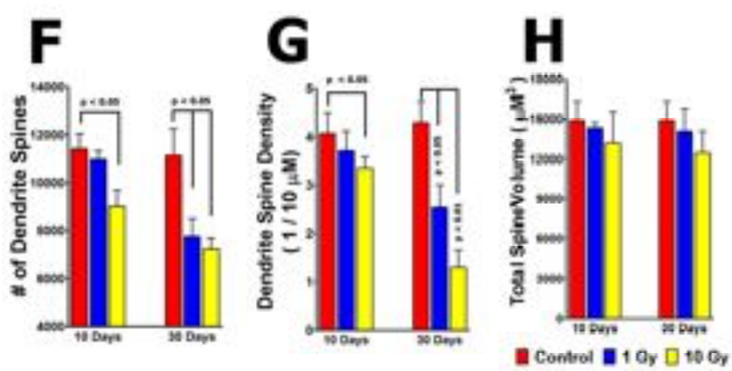

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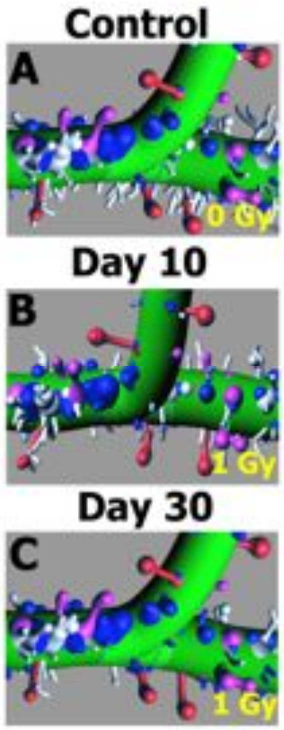
Altered spine morphology after IR



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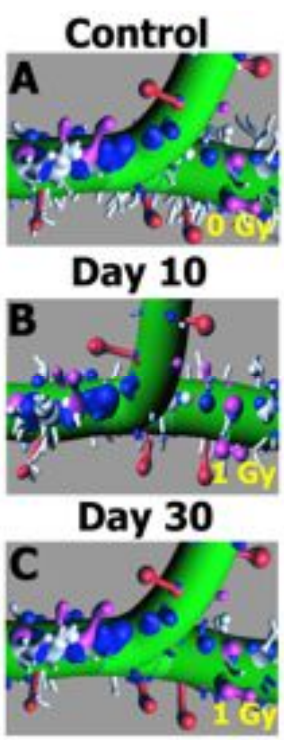

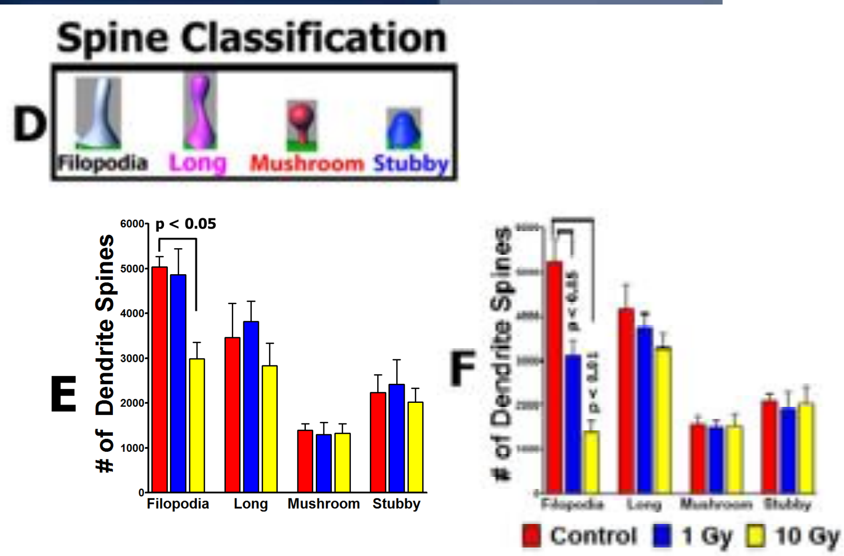

IR reduces immature **filopodia** with a smaller effect on more mature spine morphologies.

Parihar VK1, Limoli CL. Proc Natl Acad Sci U S A. 2013 Jul 30;110(31):12822-7.

Cognitive function is intimately linked to neuronal anatomy and synaptic plasticity

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- Micromorphometric analyses shows that low dose IR impacts ultrastructural features of neuronal anatomy:
  - Long-term increases in PSD95 puncta – synaptic remodeling
  - Dose-dependent reductions in synaptophysin and actin staining
  - Reduction in dendritic complexity based on a variety of morphometric parameters

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Collectively these data suggest that radiation-induced changes to **neuronal molecular anatomy** may contribute to compromised CNS functionality and impaired cognition

Conclusion I

- **Neutotoxicity is a very important side effect of radiotherapy**
- **It occurs in a dose- and time-dependent manner**
- **Its risk increases significantly with increasing radiation dose, fraction size and the subsequent administration of chemotherapy/molecular drugs**
- **The molecular mechanisms are by far from being understood**
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Current status

The aim of modern Radiooncology is cure of the patient

Role of molecular approaches are unclear in most cases

Intensification of research to understand underlying mechanisms

Conclusions & Requirements

- In addition to a lack of adequate molecular predictors, there is a tremendous lack in our knowledge about the function and relevance of particular potential cancer targets with regard to cellular radiosensitivity
- For target identification, pathophysiological models and clinically applied treatment regimes should be employed
- We need a differential evaluation and administration of molecular therapeutics in different tumor entities
- Clinical trials testing novel substances should be acccompanied by a translational research program

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