Bundesministerium
für Bildung
und Forschung

UKS
Universitätsklinikum
des Saarlandes

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Radiation-induced brain injury:

Current concepts of neurocognitive dysfunction following radiotherapy

Workshop: Individual Reponse to Ionizing Radiation, 1.- 2. September 2022, Stockholm

Radiation-induced brain injury

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Ionizing radiation (IR) at high doses → well-known risk factor for neurocognitive impairment

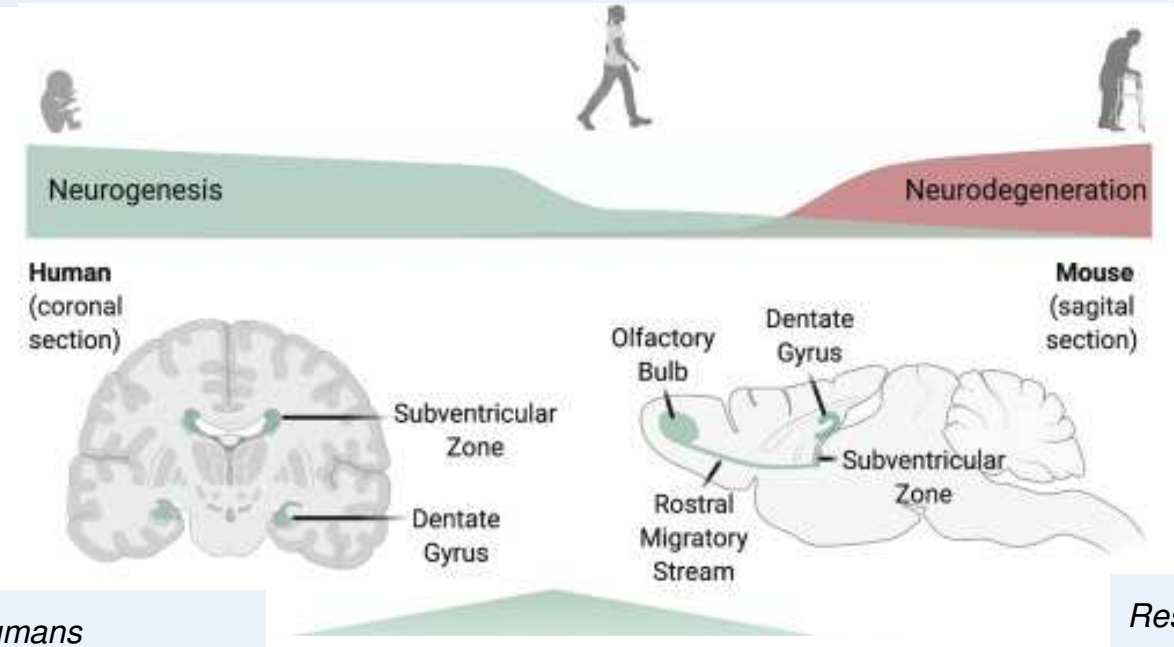
Evidence mainly based on epidemiological studies of brain cancer survivor

Definition for low-LET radiation:

- low doses: ≤ 0.1 Gy
- moderate doses: 0.1– 2 Gy

Whether low or moderate doses can also induce detrimental effects to the brain is under debate ???

Neurogenesis
→ *continuous process starting during prenatal life and extending until adulthood*



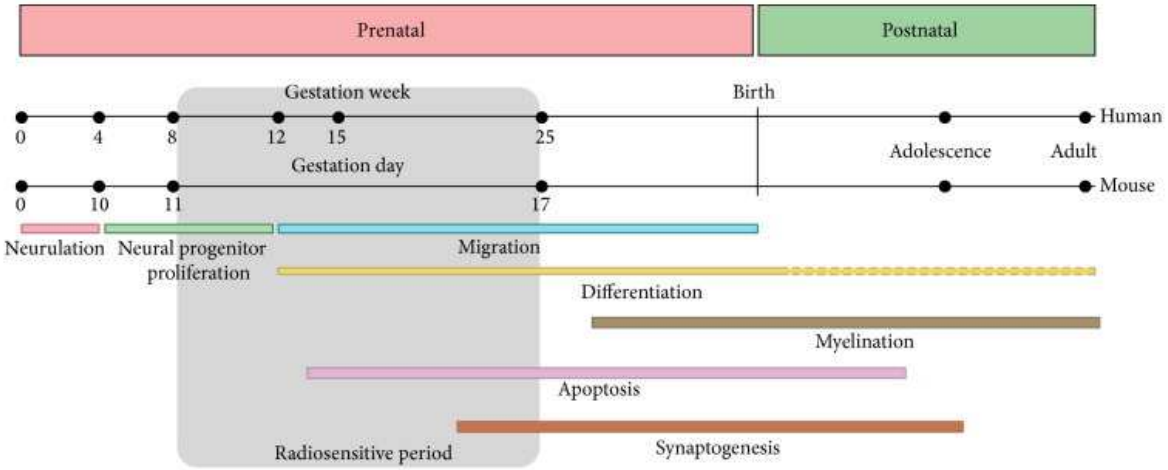
Neurodegeneration
→ *progressive loss of neurons*
(Parkinsons´s / Alzheimer´s disease)

Epidemiological studies involving humans who received low-to-moderate IR doses during gestation, childhood, adolescence, adulthood

Research studies in animal models to elucidate the mechanism of radiation-induced brain damage

Radiation-induced brain injury

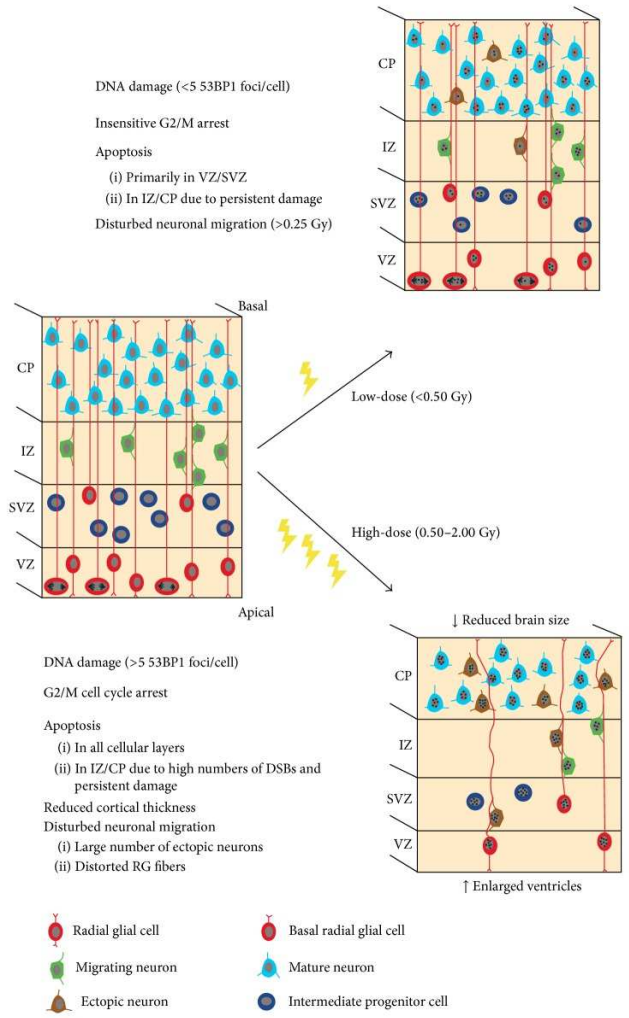
The developing brain is extremely sensitive to IR exposure, especially within specific developmental time-windows



radiation-induced DNA damage

→ apoptosis of proliferating progenitor cells

in critical phases of neurocognitive development



Verreet T, Verslegers M et al. 2016

Neurodevelopmental effects of low dose IR exposure

Radiation Effects Research Foundation, Hiroshima, Japan:

Life Span Study (**LSS**) research program investigating life-long health effects based on epidemiologic studies.

Fallout from the atomic bombing in Hiroshima and Nagasaki

Fallout from the atomic bombings in Hiroshima and Nagasaki

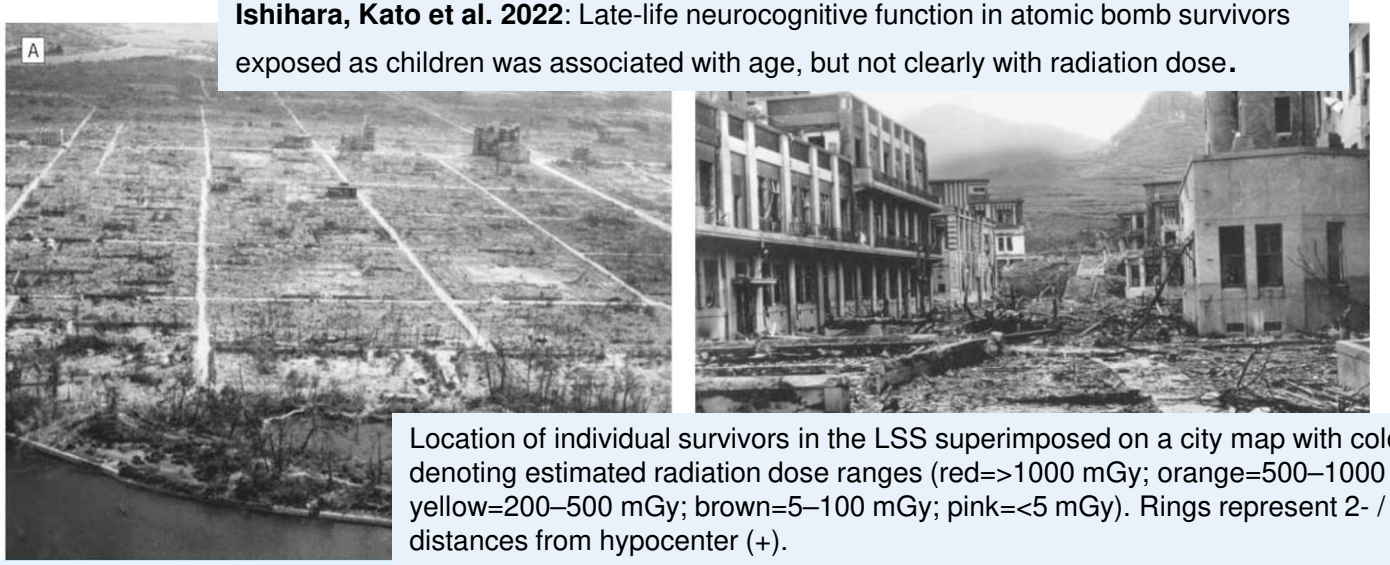
Otake et al., 1991 IQ analysis	Cohort	Atomic bomb survivors (Japan)	1,673	NR	Gamma-rays and neutrons from the atomic blast	In uterus	Fetus dose < 0.01 Gy 72%; 0.01-0.09 Gy 14.5%; 0.1-0.49 Gy 10%; 0.5-1 Gy	General cognition (IQ)	10-11 years
Otake et Sch perf							y 1 Gy	Proxy of neurodevelopment	10-11 years
Otake et SMF							y Gy	Proxy of neurodevelopment	Less than 17 years
Yoshima								Motor domains (MO)	15-16 years
							y 11%; 0.1-0.49 Gy 13%; 0.5-1 Gy 2.5%; > 1Gy 1.5%		
Yamada et al., 2015	Cohort	Atomic bomb survivors (Japan)	1,844	30%	Gamma-rays and neutrons from the atomic blast	> 13 years old (Maximum 33 years old)	Mean (SD): 434 (727) mGy; 15% above 1 Gy brain dose	General cognition (CASI score)	Between 60 and 80 years old

Individuals exposed in utero to atomic bomb radiation

→ disturbed brain development with mental retardation

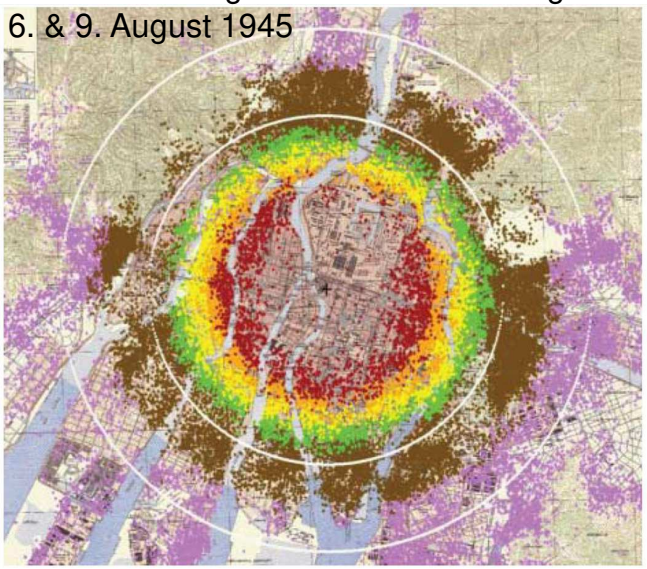
→ highest risks during weeks 8–15 of gestation.

Ishihara, Kato et al. 2022: Late-life neurocognitive function in atomic bomb survivors exposed as children was associated with age, but not clearly with radiation dose.



Location of individual survivors in the LSS superimposed on a city map with color denoting estimated radiation dose ranges (red=>1000 mGy; orange=500–1000 mGy; yellow=200–500 mGy; brown=5–100 mGy; pink=<5 mGy). Rings represent 2- / 3-km distances from hypocenter (+).

Atomic bombing in Hiroshima and Nagasaki
6. & 9. August 1945



Neurodevelopmental effects of low dose IR exposure

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Medically exposed population

→ mainly historical research collectives

	Methods				Exposure			Outcome	
Reference	Study design	Study population and location	Sample size	Sex (Male %)	Type of exposure	Age at exposure	Dose distribution	Outcome	Age at outcome measurement
Medically exposed population									
Ron et al., 1982	Cohort	Tinea capitis cohort (Israel)	27,084 (10842 irradiated matched to 10,842 controls and to 5400 siblings)	49%	Radiotherapy for benign disease	Mean = 7 years	Mean brain dose ranged from 0.7 to 1.6 Gy (Ron et al., 1988)	General cognition (score of military test); Proxy (education achievement; mental diseases)	10-20 years for education achievement analysis; 17 years for IQ; 9-34 for mental diseases
Hall et al., 2004	Cohort	Cutaneous haemangioma cohort (Sweden)	2,816	100%	Radiotherapy for benign disease	Mean = 7 months	Median dose to the brain = 20 mGy (range 0-2800 mGy)	General cognition & cognitive domains [V,I.] (score of military test); Education achievement	18 years
Zeltzer et al., 2008	Cohort	Childhood cancer survivors (United States and Canada)	7,147	49%	Radiotherapy for malignant disease	Median = 7 years (range 0-20)	No radiotherapy 33.6%; Radiotherapy other then cranial 35%; Cranial radiotherapy 30%	Socio-emotional domains (Self-reported test)	32 years (median)
Krull et al., 2012	Cohort	Childhood HL survivors (United States)	62	NR	Radiotherapy for malignant disease	Mean = 15 years	39% < 30 Gy and 61% > 30 Gy to the thorax (*)	General cognition; brain pathological features (MRI)	42.2 years
van der Geest et al., 2013	Cohort	Childhood cancer survivors (The Netherlands)	1,092 (652 childhood cancer survivors; 440 controls)	56%	Radiotherapy for malignant disease	Median = 6 years	7% of survivors received limbs/ abdomen radiotherapy (very low brain dose)	Socio-emotional domains (self-reported test)	23 years (median)
Blomstrand et al., 2014	Cohort	Cutaneous haemangioma cohort (Sweden)	3,030	100%	Radiotherapy for benign disease	Median = 5 months	Median dose to the brain = 20 mGy	General cognition & cognitive domains [V, I.] (score of military test); Education achievement	18 years
Nordenskjöld et al., 2015	Cohort	Maternal x-ray pelvimetry cohort (Sweden)	46,066	51%	Diagnostic x-ray exposure	In uterus	3.5% exposed to pelvimetry (estimated fetal dose 1.5 mGy)	Education achievement	15 years
Salonen et al., 2018	Cohort	CT scan exposed cohort (Sweden)	147	54%	Diagnostic x-ray exposure (CT-scan)	Mean = 11 years (2.77y)	For a single head CT-scan, the estimated brain dose is 30 and 50 mGy (Lee et al., 2018).	Cognitive domains [A, E, LM, P, V]; Motor domain	17.8 years

Radiotherapy for benign disease:

- Tinea capitis cohort
- Cutaneous haemangioma cohort

Diagnostic X-ray exposure:

- Maternal X-ray pelvimetry/
- CT scan exposed cohort

Radiotherapy outside the brain/ head

- Childhood Cancer Survivor

Neurodevelopmental effects of low dose IR exposure

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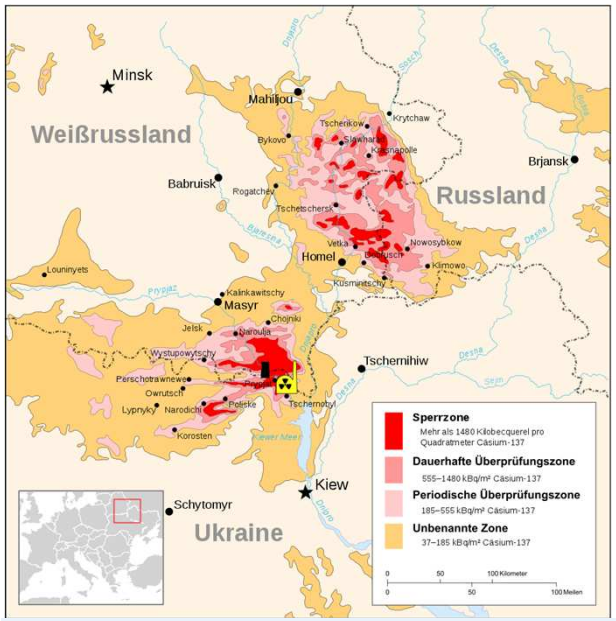
Reference	Methods: Study design	Study population and location	Sample size	Sex (Male %)	Exposure: Type of exposure	Age at exposure	Dose distribution	Outcome: Outcome	Age at outcome measurement
Environmental disaster exposure									
Nyagu et al., 1998	Cohort	Chernobyl evacuees (Ukraine)	1,339	52%	Evacuees (30 km zone) & children living in strict control zones and moderate contamination areas (with Cs deposition density > 37 kBq/m^2) (#)	In uterus	40% in the exposed group (21% of which were evacuees, 43% residents of contaminated areas), 60% from clean territories	General cognition (IQ), Social-emotional (parent reporting)	6-8 years old
Loganovskaja and Loganovsky, 1999	Cohort	Chernobyl evacuees (Ukraine) (randomly selected from Nyagu (1998))	100	53%	Evacuated from the 30 km exclusion zone of Chernobyl power plant (#)	In uterus	50% evacuee; 50% non-exposed	General cognition (IQ), Social-emotional (parent reporting, emotional/ behaviour disorders)	9-10 years
Igumnov and Drozdovitch, 2000; Kolominsky et al.,	Cohort	Chernobyl evacuees (Belarus)	500	51%	Evacuated in 1991–93 from areas with a ^{137}Cs soil deposition density ranging from 100 to 15400 kBq/m^2	In uterus	50% evacuees (< = 3 Gy to the thyroid) living in Minsk; 50% non-evacuee (Cs deposition	General cognition (IQ), Social-emotional and motor domain	6-7 year (First exam); 10-12 years (Second exam)
Bromet et a Litcher 2000; et al.,									
Bar Joseph		exposed emigrants (Israel)			other Belarus areas contaminated with ^{137}Cs	4 years at the time of the accident	deposition density: 40 to 1480 kBq/m^2). Others from area with < 37 kBq/m^2		
Almond et al., 2009	Cohort	Chernobyl fallout exposure (Sweden)	562,637	NR	Born between 1983 and 1988 in areas of Sweden with different contamination levels	In uterus	3% from highly contaminated area (^{137}Cs deposition density: 44.2 kBq/m^2). Highest dose to Swedish population estimated to be 4 mGy (Edvarson and Moberg, 1991)	Proxy (School achievement)	16 years
Heiervang et al., 2010a, 2010b	Cohort	Chernobyl fallout exposure (Norway)	178	49%	Norway residents born soon after the Chernobyl accident. Mean external radiation estimate for the exposed areas is 0.935 mSv	In uterus or < 18 months	48% of participants were residents in the most contaminated areas (average dose 0.94 mGy; the comparison group lived in areas of low contamination (average dose 0.01 mGy)	Heiervang et al., 2010a: General cognition (IQ) & cognitive domains [I., V]; Heiervang et al., 2010b: Cognitive domains [A, E, I., P,V]	Median 18.4 years (range 16.3-20 y)
Black et al., 2013	Cohort	Nuclear weapon testing in the Russian Arctic Archipelago 1955-62 (Norway)	603,294	49%	Born between 1956 and 1966. Residents of areas with different contamination levels	In uterus (8-16 weeks of gestation)	Mean (SD) total beta radiation ground deposition for the men sample: 59.76 (91.01) kBq/m^2); for women: 64.77 (98.39) kBq/m^2	General cognition (score of military test); Education achievement	Adolescence to young adulthood
							exposed group		
Lie et al., 2017	Cohort	Chernobyl fallout exposure (Norway)	166,967 exposed 148,744 non-exposed	NR	Exposure during the 5th gestational month	In uterus	Exposed category: < 0.01 mSv 52.5%; 0.01-0.015 31.7%; 0.016-0.023 mSv 11%; > =0.024 mSv 5.2% (# #)	Proxy (mental disorder prevalence, school achievement)	Mental retardation (5 years); high school completion (20 y), school grade (16 y)

2006 WHO report: Health Effects of the Chernobyl Accidents

No damage to the brain development of unborn babies and infants through IR exposure from the Chernobyl disaster

Difficulties in determining and reconstructing levels of external and internal radiation doses !

Chernobyl accident 26 April 1986



Fallout: radioiodine (^{131}I) & radiocaesium (^{137}Cs)
→ **relative low doses (0.01- 0.25 Sv)**
prenatally irradiated children → cognitive impairments?
inconsistent findings → ongoing debate !

Environmental disaster exposure

World Health Organization (WHO)

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR)

Since 1980´s, average annual IR dose to the general population has nearly doubled

→ **increase in medical radiation exposure** (NCRP Report No. 160, 2009; UNSCEAR 2021, 2013, 2008)

National Council of Radiation Protection and Measurement (NCRP)

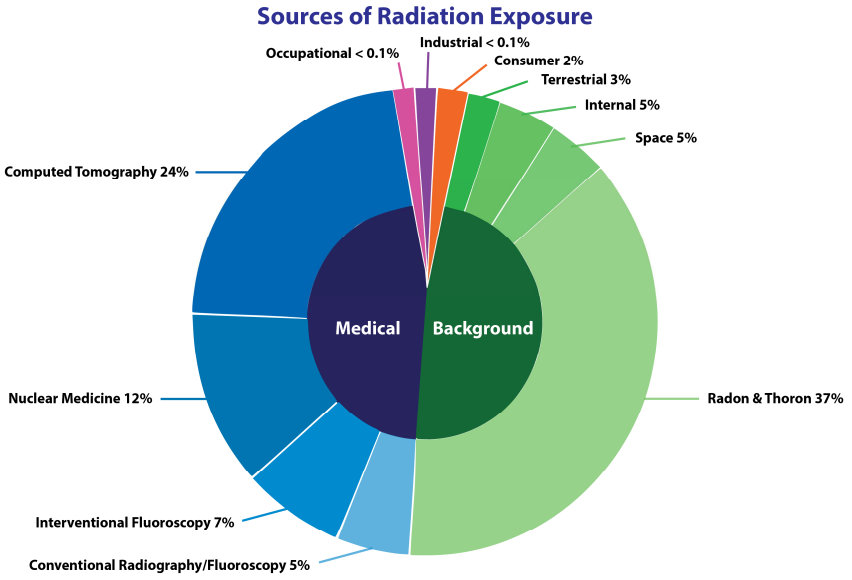
Diagnostic imaging → *Computed Tomography*
→ increased risk for brain cancers

- Increased brain tumor incidence in pediatric patients exposed to head CTs.
- Children → more susceptible to radiation-induced cancer than adults
- → longer life expectancy for potential cancer development

Sheppard, Nguyen et al. 2018

→ head CT examination at the age of 6-16 years
→ no effect on later cognitive functions

Salonen, Nyman et al. 2018



Average Annual Radiation Dose

Sources	Radon & Thoron	Computed Tomography	Nuclear Medicine	Interventional Fluoroscopy	Space	Conventional Radiography/ Fluoroscopy	Internal	Terrestrial	Consumer	Occupational	Industrial
Units											
mrem (United States)	228 mrem	147 mrem	77 mrem	43 mrem	33 mrem	33 mrem	29 mrem	21 mrem	13 mrem	0.5 mrem	0.3 mrem
mSv (International)	2.28 mSv	1.47 mSv	0.77 mSv	0.43 mSv	0.33 mSv	0.33mSv	0.29 mSv	0.21 mSv	0.13 mSv	0.005 mSv	0.003 mSv

(Source: National Council on Radiation Protection & Measurements, Report No. 160)

Radiotherapy (RT) → effective treatment modality
for patients of all ages with malignant & benign brain tumours

→ *clearly higher doses to healthy brain tissue…*

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Before the era of conformal radiotherapy … → ***severe radiation-induced CNS toxicities***

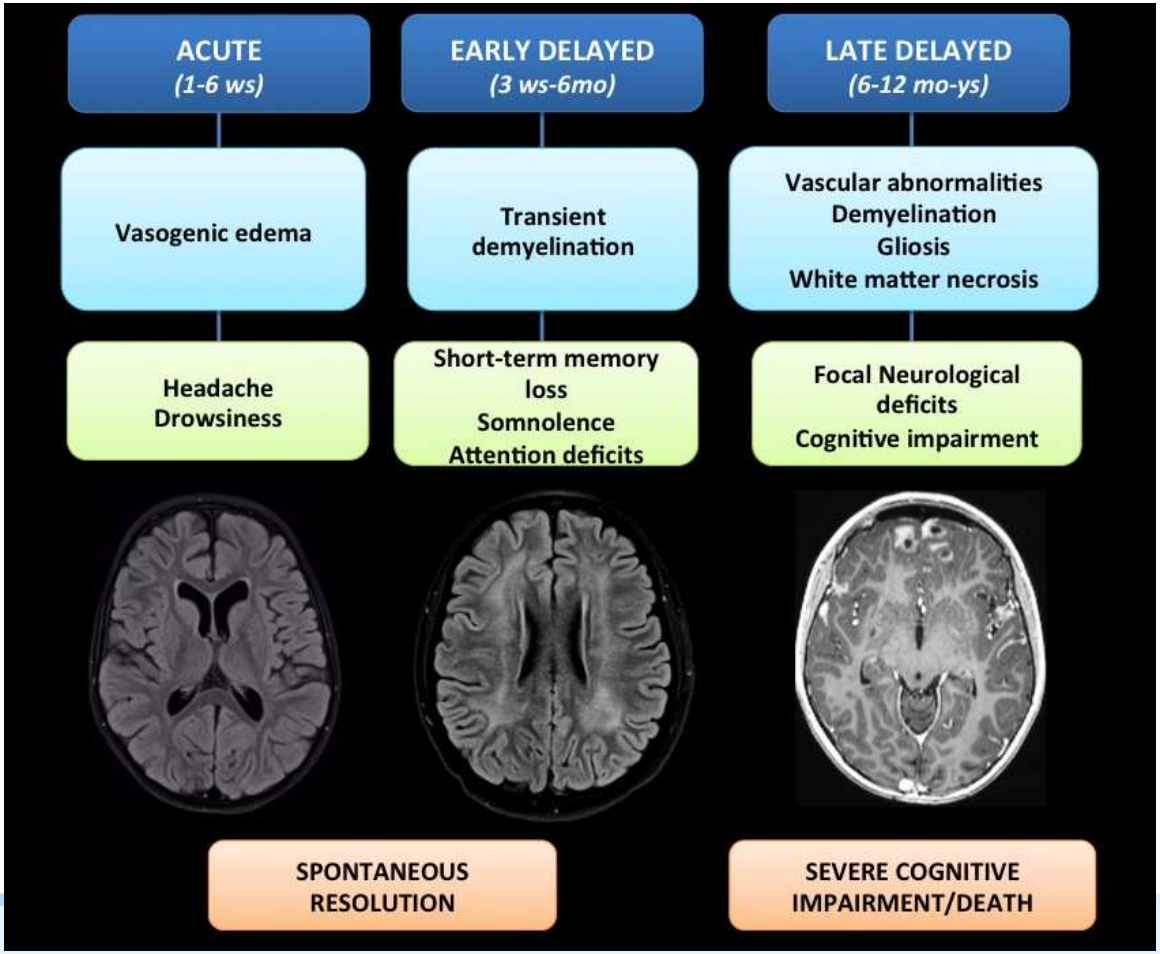
- whole-brain RT → entire brain and brainstem
- partial-brain RT → tumour or tumour bed & surrounding margin

→ large areas of healthy brain exposed to high doses

Increased conformality of modern RT techniques

- 3D Conformal Radiotherapy
- Intensity-modulated Radiotherapy (IMRT)
- Image-Guided Radiotherapy (IGRT)
- Tomotherapy
- Stereotactic Radiosurgery

→ significantly less serious CNS toxicities



Conformal radiotherapy (RT) → *brain cancer patients*

→ *fractionated RT* → *repetitive IR exposure*

→ high cumulative doses to the tumour (≈ 60 Gy)

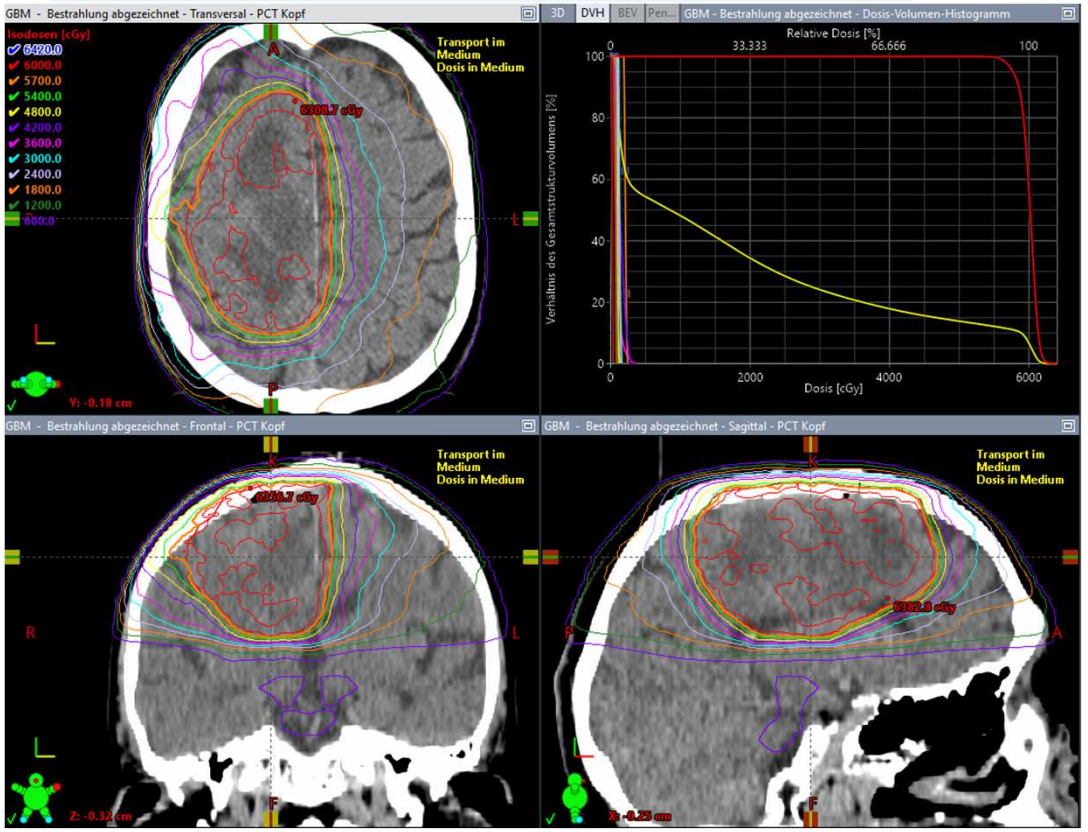
→ low-to-moderate doses to healthy brain tissue

→ dose distribution depends on the RT technique

In last 20 years, the use of 3D conformal radiotherapy reduced the amount of brain tissue treated to high-dose levels.

→ opportunity to minimize RT injury to healthy brain substructures critical for neurocognitive function

Glioblastom grade IV:
RT planning with dose-volume-histogram



90% isodose encloses the target volume→ dose homogeneity in tumor
large volumes of healthy brain → exposed to low-moderate doses

Childhood cancer survivors

→ frequently experience cognitive dysfunction months to years after RT

Childhood brain tumors → low-grade glioma & medulloblastoma
→ most frequently observed brain tumours in children with high survival rates

Mulhern, Merchant et al. 2004
Castellino, Ullrich et al. 2014

Children receiving RT for their cancer → greater cognitive impairment than those who undergo surgery and/or chemotherapy without IR

Merchant, Conklin et al. 2009
Padovani, Andre et al. 2012

RT doses and field sizes → highly associated with development of cognitive dysfunction

Packer 2002

Younger age at treatment is the most important patient-related risk factor

Meadows, Gordon et al. 1981,
Duffner 2010

Due to treatment modifications → prevalence and severity of cognitive dysfunction in survivors of childhood cancer has declined over the last decades

Duffner 2004,
Mabbott, Spiegler et al. 2005
Castellino, Ullrich et al. 2014

Acute lymphatic leukaemia (ALL)

With realization that cranial RT in ALL is causally related with IQ decline

→ dose of prophylactic RT was systematically reduced and

eventually RT was completely removed from therapy regimes

Pui and Howard 2008
Richards, Pui et al. 2013

Adult cancer survivors: relationship between RT & cognitive dysfunction

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Brain tumour survivors irradiated as adults
→ progressive cognitive dysfunction and accelerated cognitive decline

High-grade Glioma (50% of all primary brain tumors)

most aggressive malignant primary brain tumor → poor prognosis

Scoccianti, Detti et al. 2012

Metastatic Brain Tumors
→ mainly from lung and breast cancer, or melanoma

→ due to early tumor progression no long-term effects on neurocognitive function can be recorded

Low-grade Glioma:
→ prolonged survival → experience neurocognitive impairment from RT

Olson, Riedel et al. 2000
Surma-aho, Niemela et al. 2001
Postma, Klein et al. 2002
Correa, Shi et al. 2008,
Douw, Klein et al. 2009

→ most studies evaluating the relationship between RT and cognitive impairment

prospective trials: neurocognitive deficits → multifactorial genesis !

Armstrong, Hunter et al. 2002
Klein, Heimans et al. 2002
Brown, Buckner et al. 2003
Laack, Brown et al. 2005

→ **tumour-related factors and other treatment-related factors**

Cancer survivors: relationship between RT & cognitive dysfunction

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Literature review

adequate follow-up
of several years
only in patients with
- low-grade glioma
- pediatric brain tumors

Sr. No.	Type of Cancer Survivors	No. of Patients Exposed	Average Age (Years)	Type of Radiotherapy Given	Convalescence after Exposure (Median Time)	Impact/Outcome	Ref.
1	Metastatic brain cancer survivors	28	64	Stereotactic radiosurgery (20 Gy) + WBRT 30 Gy (12 fractions of 2.5 Gy per day)	4 months	Verbal learning and memory decline	[62]
2	With and without metastatic brain cancer survivors	44	43	WBRT - 40 Gy (20 fractions)	6-8 weeks	Verbal memory decline	[109]
3	Metastatic brain	81	65	WBRT 40 Gy (2 Gy five times a	4 weeks	Cognitive decline	[110]
4	Low grade glioma survivors	32	41	Focal radiotherapy/ WBRT 30-69 Gy (21-43 fraction of 2Gy)	12 years	Cognitive decline	[111]
5	Primary brain tumour survivors	57	47	Partial/ whole brain irradiation 10, 40 and 60 Gy (1.8-2.0 Gy/fraction)	6 months	Cognitive decline	[112]
6	Benign or low-grade adult brain tumor survivors	29	56	Fractionated stereotactic radiotherapy 50.4-54 Gy (28-30 fractions of 1.8 Gy)	18 months	Verbal memory decline	[113]
7	Low-grade glioma survivors	78	9.7	Cranial radiotherapy 54 Gy (1.8 Gy per fraction)	6 weeks	Cognitive decline and hearing loss	[114]
8	Breast cancer survivors	51	47	Adjuvant regional radiotherapy 50 Gy (25 treatments)	7 months	Verbal memory decline and delayed recall index	[115]
9	Nasopharyngeal cancer survivors	102	56	Intensity-modulated radiotherapy 70 Gy (35 fractions of 2 Gy)	7.5 years	Neurocognitive impairment and clinically significant apathy, disinhibition and executive dysfunction	[116]
10	Head and Neck Cancer Survivors	80	59	70 Gy in 35 fractions	2 years	Neurocognitive sequelae	[117]
11	Primary brain lymphoma survivors	118	52	WBRT five fractions of 180 cGy per week	2 years	Cognitive impairment	[118]
12	Pediatric brain tumor survivors	39	12	Proton beam radiotherapy 55.80 Gy for craniospinal and 50.40 Gy for focal irradiation	>2 years	The decline in Attention, processing speed and executive functioning	[119]
13	Pediatric brain tumor survivors	224	26	Craniospinal irradiation 35.2 Gy and whole brain radiation 23.4 Gy	18 years	Severe neurocognitive impairment	[120]
14	Nasopharyngeal cancer survivors	100	50	Intensity-modulated radiotherapy	5 years	Cognitive functioning, social functioning, fatigue, neuropathy, hearing loss, dysphagia, xerostomia, and neck fibrosis	[121]

Adult cancer survivors: relationship between RT & cognitive dysfunction

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prophylactic whole-brain radiotherapy

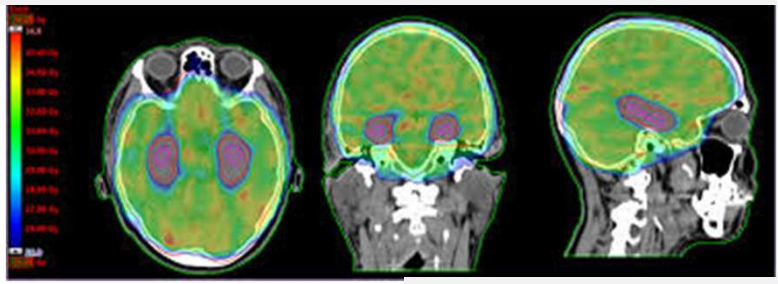
→ to prevent or delay the spread of cancer cells to the brain

standard care for ***small-cell lung cancer***
showing complete response to front-line chemotherapy

recent clinical trial: prophylactic whole-brain RT for small-cell lung cancer
→ no survival benefits but increased risk of neurocognitive decline affecting quality of life

Halthore, Goenka et al. 2018

Reducing radiation dose to the hippocampus with hippocampal avoidance prophylactic cranial irradiation (HA-PCI) → to prevent cognitive decline



de Ruiter, Groot et al. 2022

Total-body irradiation → allogeneic bone marrow transplantation for haematological malignancies

cumulative doses ≤12 Gy → cognitive deficits in long-term survivors

Harder, Duivenvoorden et al. 2006

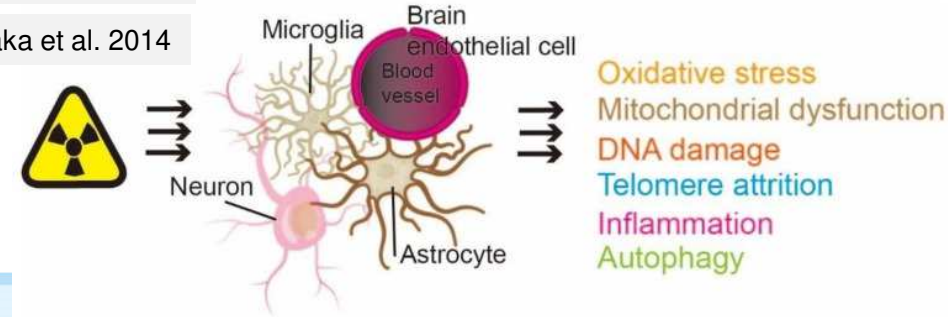
Neurodegeneration

Radiation-induced brain injury → premature brain aging ?
→ may predispose to neurodegenerative disorders ?
including Alzheimer´s and Parkinson´s disease

Wang, Yin et al. 2021

Begum, Wang et al. 2012

Wang, Tanaka et al. 2014



LSS on A-bomb survivors → no effect of IR exposure on cognitive decline at older age

Yamada et al. 2016 & 2019

Analyses of radiation risks are underway, but not yet available

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Treatment variables defining RT-related neurotoxicity

- **total and fractional doses**
- **extent of target volumes**
- **localization of target fields**
- **RT techniques**

Olson et al., 2000
Postma et al., 2002
Surma-aho et al., 2001
Correa et al., 2008;
Douw et al., 2009

Additional causes of neurocognitive decline

- **tumour-related factors**

(tumour localisation, tumour size and histology, disease progression)

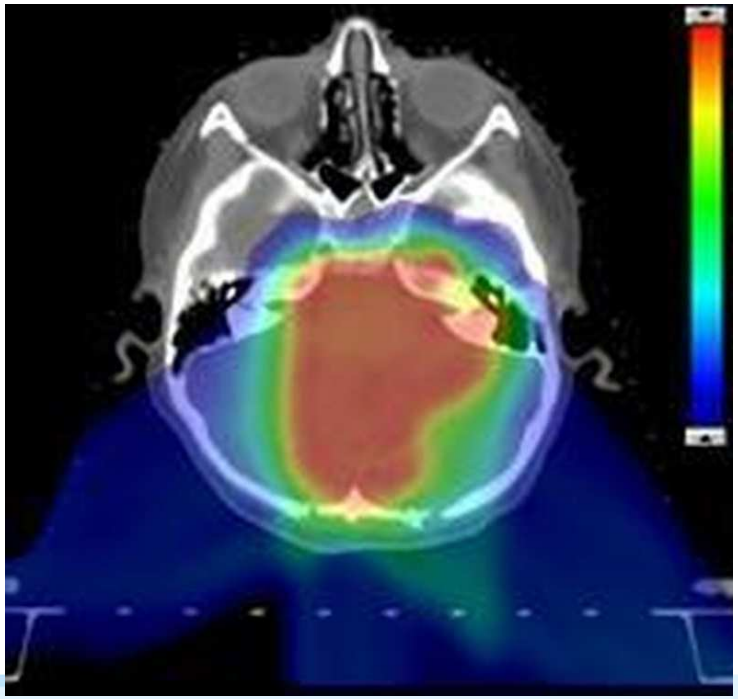
- **other treatment-related factors**

(neurosurgery, use of anti-epileptic drugs, parenteral or intrathecal chemotherapy multiple exposures to anesthesia)

- **patient-related factors**

(age at treatment, pre-existing co-morbidities)

Data interpretation often difficult
→ impossible differentiation between adverse side effects of RT from underlying cancer disease or concomitant tumour therapy



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Strong heterogeneity across studies with regard to radiation exposure and outcome assessment

Following information is required for a clear assessments

- **Radiation exposure type** (e.g. radiotherapy techniques, accidental or diagnostic exposure)
- **Radiation exposure metrics** (e.g. radiation quality, prescribed/ exposed dose, mean organ dose, effective dose)
- **Exposure data source** (e.g. medical records, scientifically-based calculations, determined dosimetrically)

Cognitive dysfunction → symptom complex characterized by

- decline in full scale intelligence quotient (IQ)
- impairment in core functional domains
- behavioural changes

→ compromise social / academic performance and quality of life

→
- attention or vigilance
- working memory
- executive functioning (e.g. planning and organization)
- information processing speed
- visual-motor integration
- learning deficits, etc.

Problems with neurocognitive testing:

- lack of standardised and validated examination methods
- missing neurocognitive pre-treatment status
- reduced patient compliance

→ **Standardized psychometric tests**
→ to detect subtle deficits
in intelligence or neurodevelopmental function.

→ high risk of bias, lack of internal and/or external validation

Radiation-induced brain injury

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With all confounding factors in epidemiological studies

→ difficult to draw clear conclusions

No mechanistic insights can be gained from epidemiological studies !

Preclinical mouse models are needed to work out

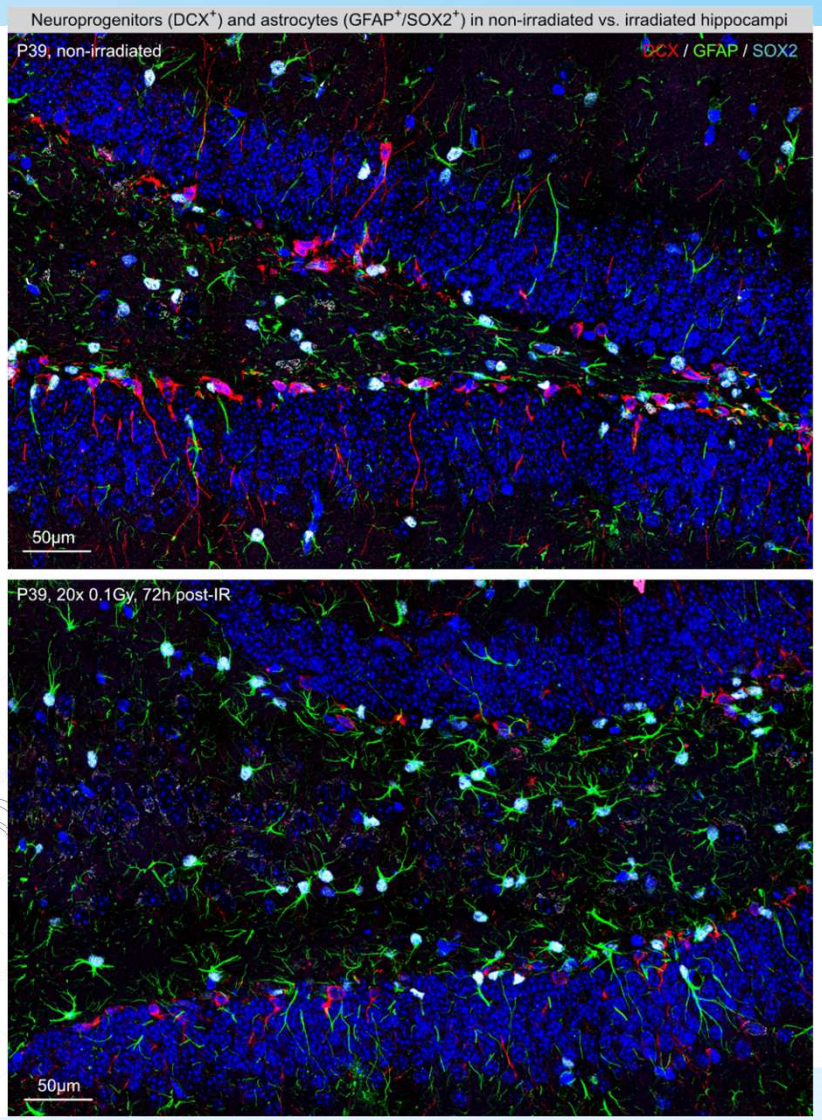
→ complex pathomechanisms of radiation-induced brain damage

→ clear dose concepts for radiation protection

RT → ø single radiation event

Effect of repetitive low-dose IR exposure on specific brain substructures

→ mouse model with fractionated low-dose radiation (LDR)

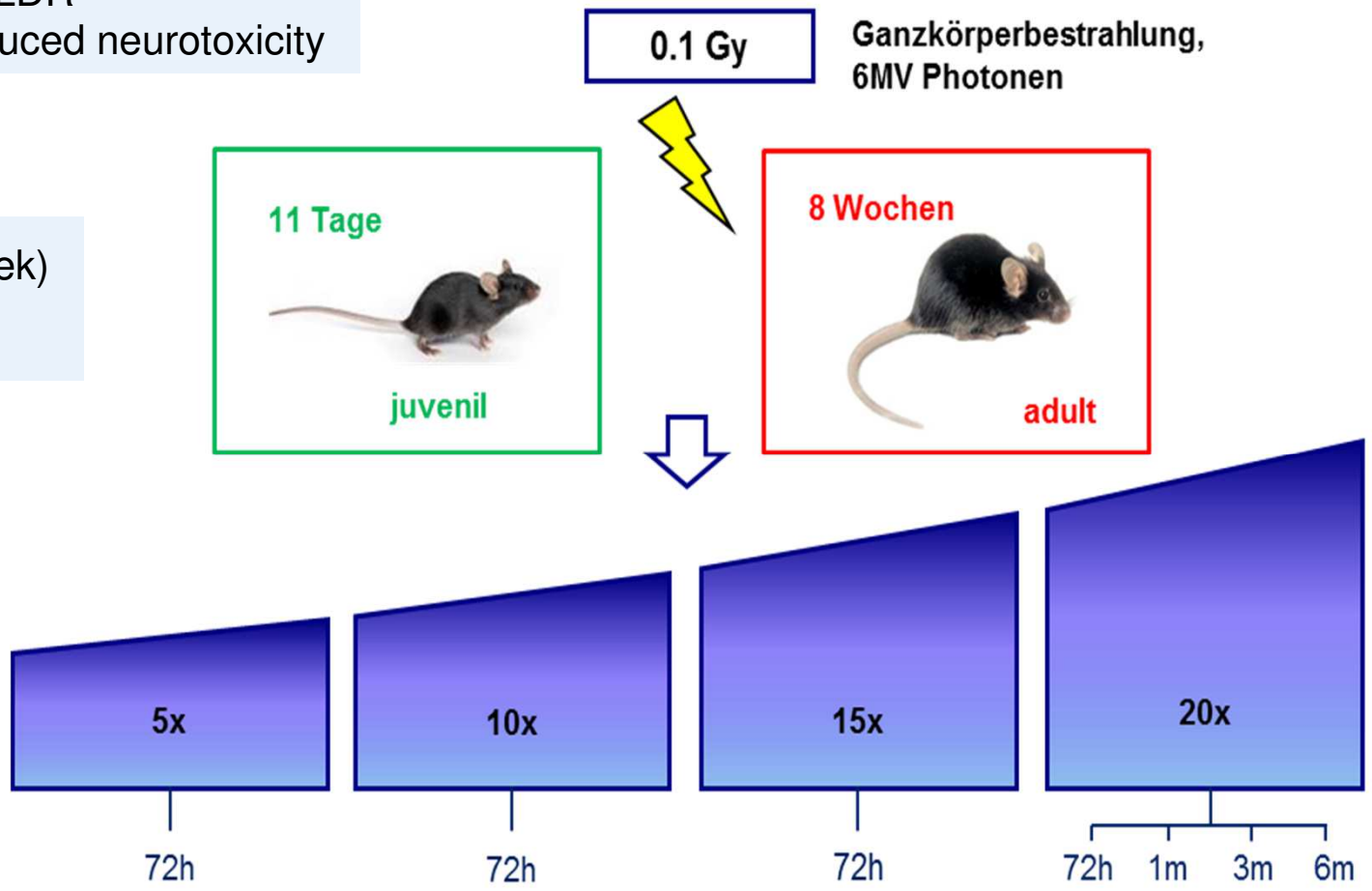


Fractionated low-dose radiation (LDR)

preclinical *in-vivo* model with daily LDR
→ pathophysiology of radiation-induced neurotoxicity

daily (Monday to Friday: 5x per week)

whole-body irradiation with 0.1Gy



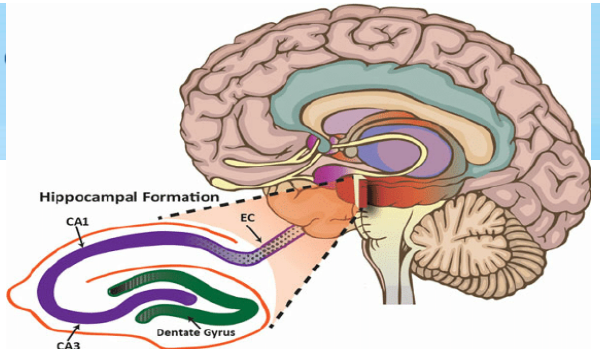
number of fractions

time-points of analysis
after fractionated LDR

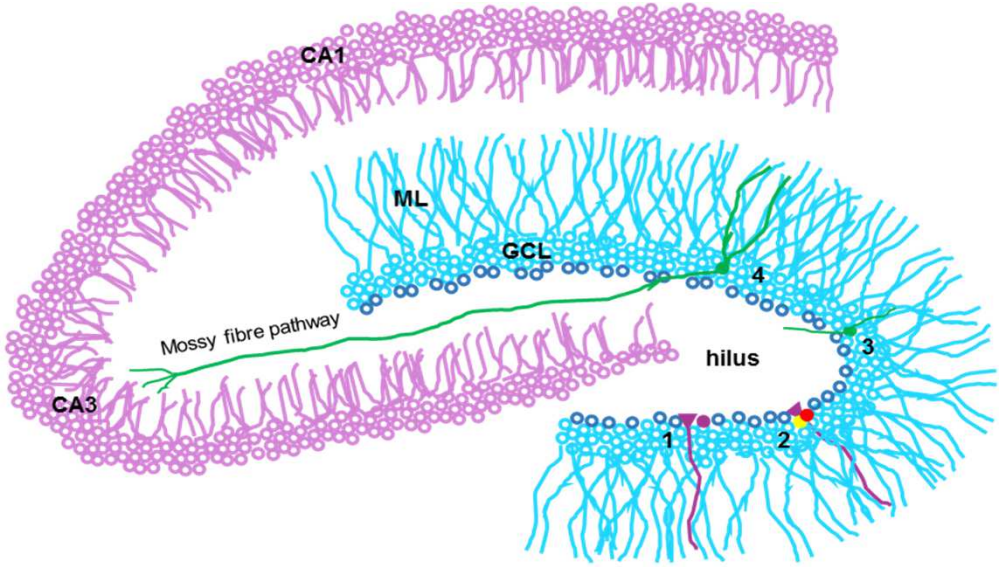
→ long-terms effect

Adult neurogenesis in the hippocampal stem cell niche

→ generation of new neurons from neural stem cells throughout life
in the subgranular zone (SGZ) of hippocampal dentate gyrus

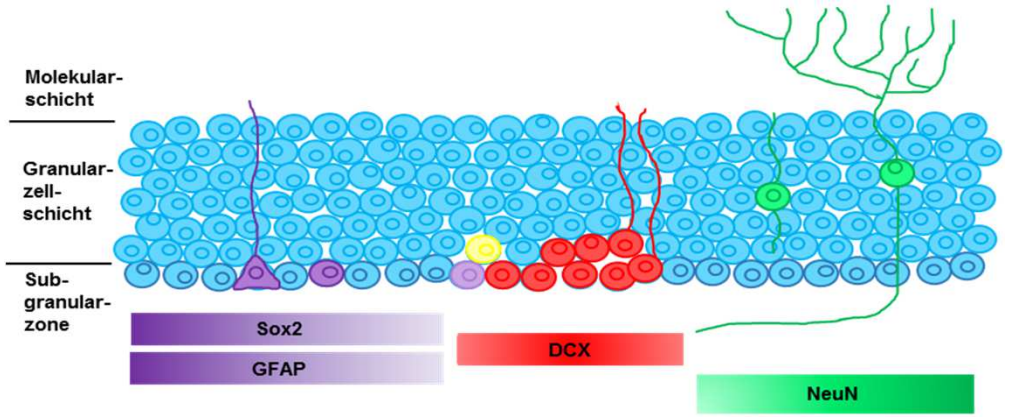


Hippocampus
→ consolidation of information
from short-term to long-term memory



- SGZ: adulte neurale Stammzellen
- GCL: Vorläuferzellen & granuläre Neuronen
- CA: Pyramidenzellen

- adulte neurale Stammzellen
- Typ2a-Vorläuferzelle
- Typ2b-Vorläuferzelle
- Neuron



neural stem cells | proliferating progenitors | post-mitotic neurons

specific markers identify subpopulations
→ during different stages of neurogenesis

Radiation-induced DNA damage: Quantification of DNA damage foci

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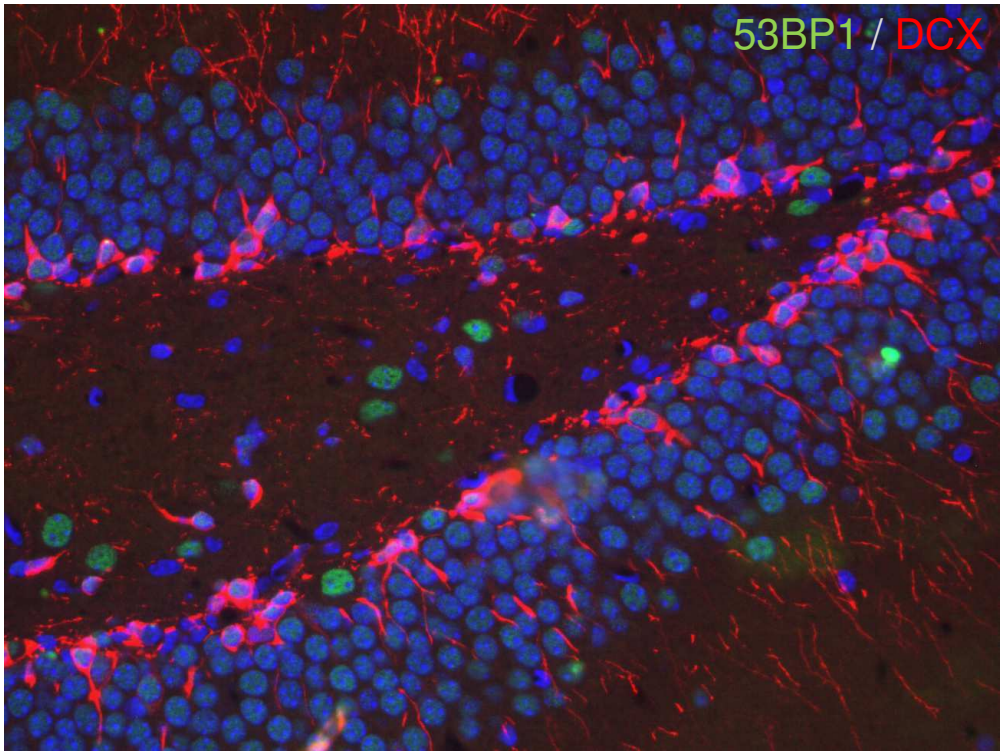
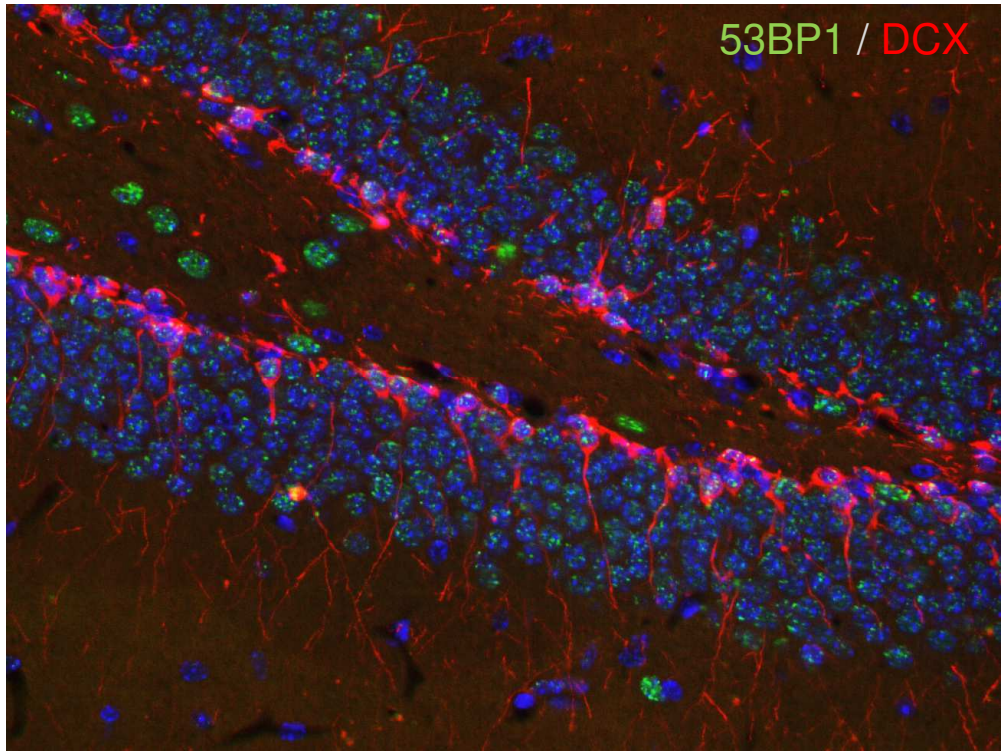
Gyrus dentate: non-irradiated versus irradiated (2Gy, 0.5h post-IR):





Radiation-induced DNA damage → quantification of 53BP1-foci within hippocampal neurons.

Radiation-induced DNA damage: persisting DNA damage foci

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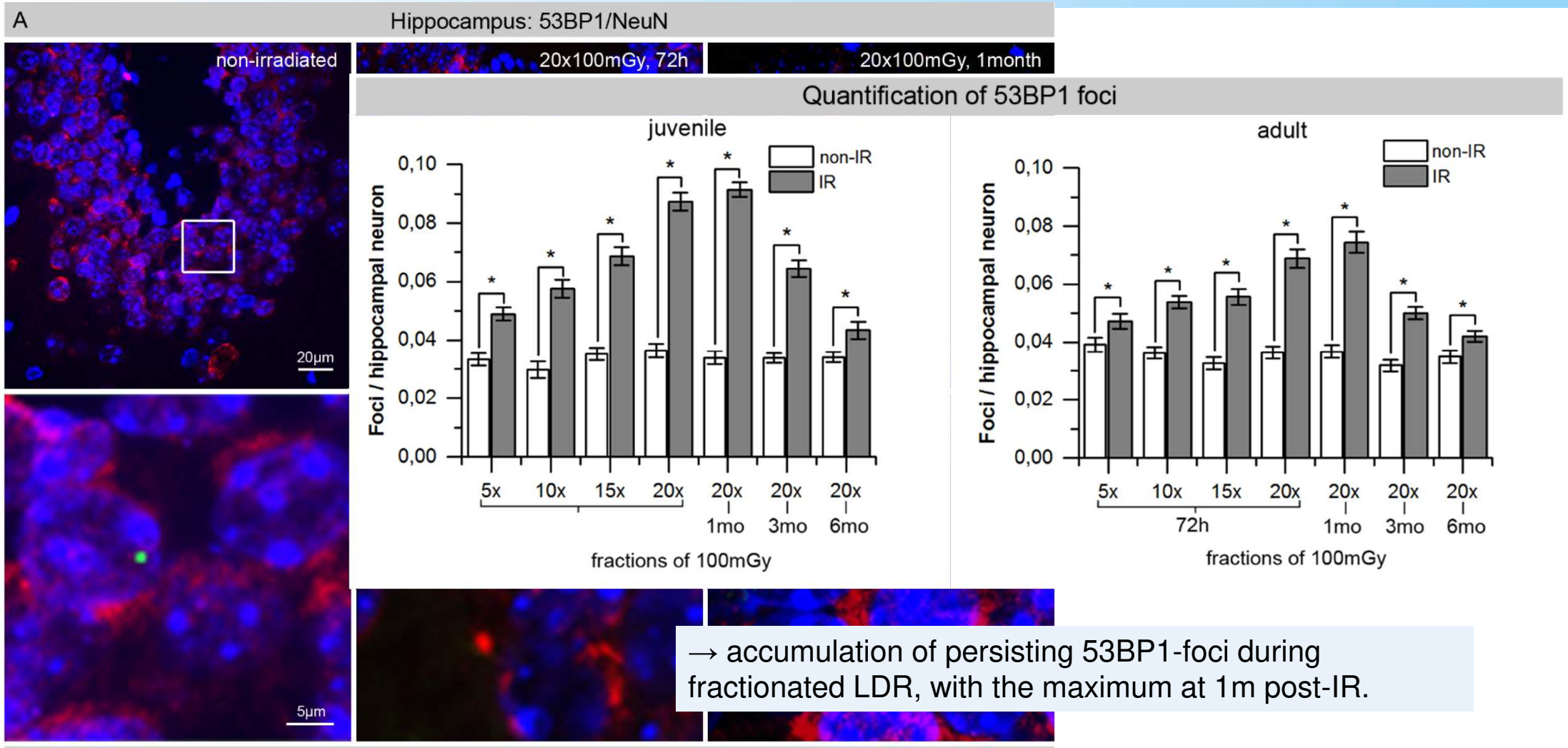
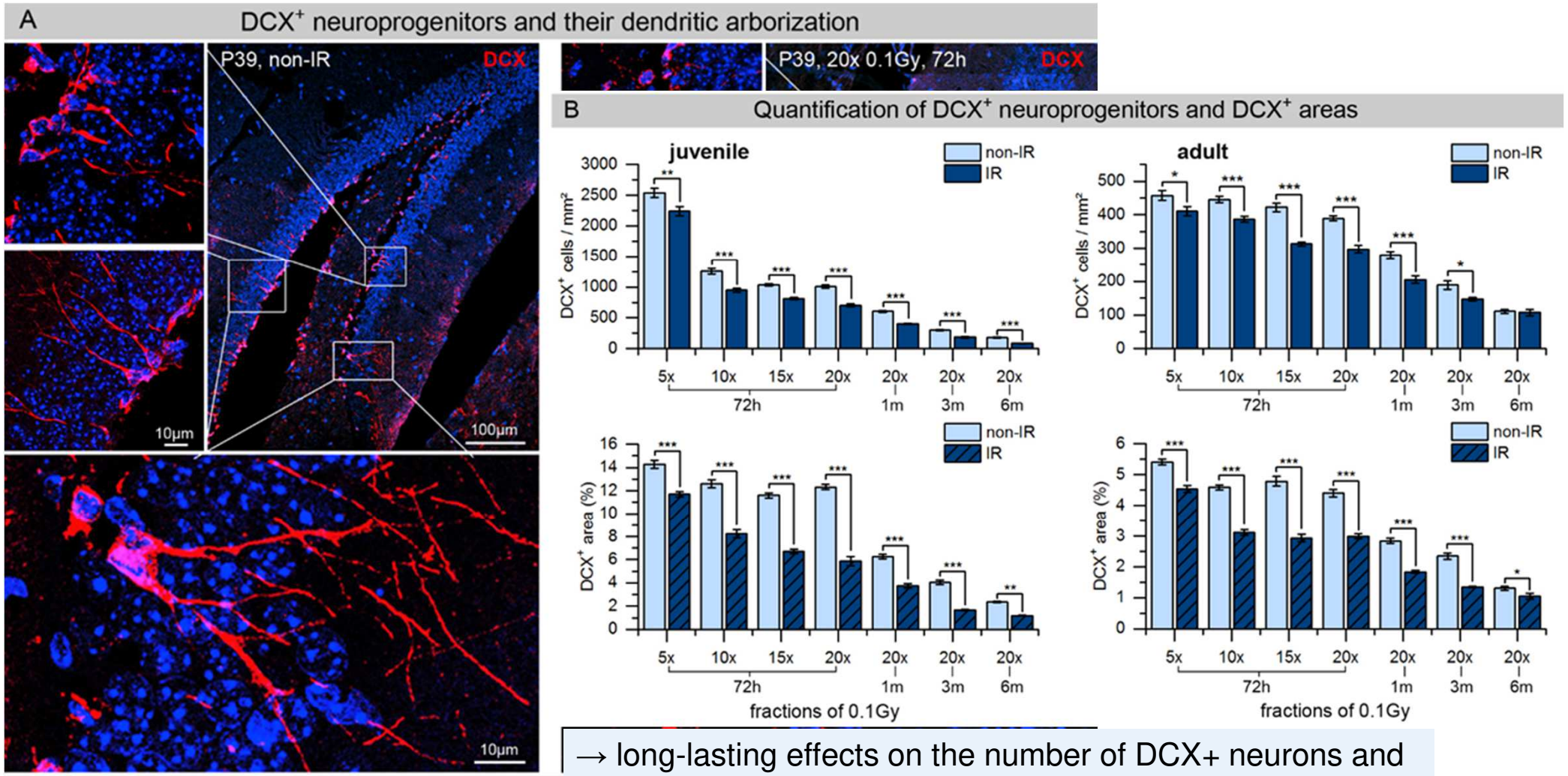


→ accumulation of persisting 53BP1-foci during fractionated LDR, with the maximum at 1m post-IR.

Schmal, Isermann et al. 2019

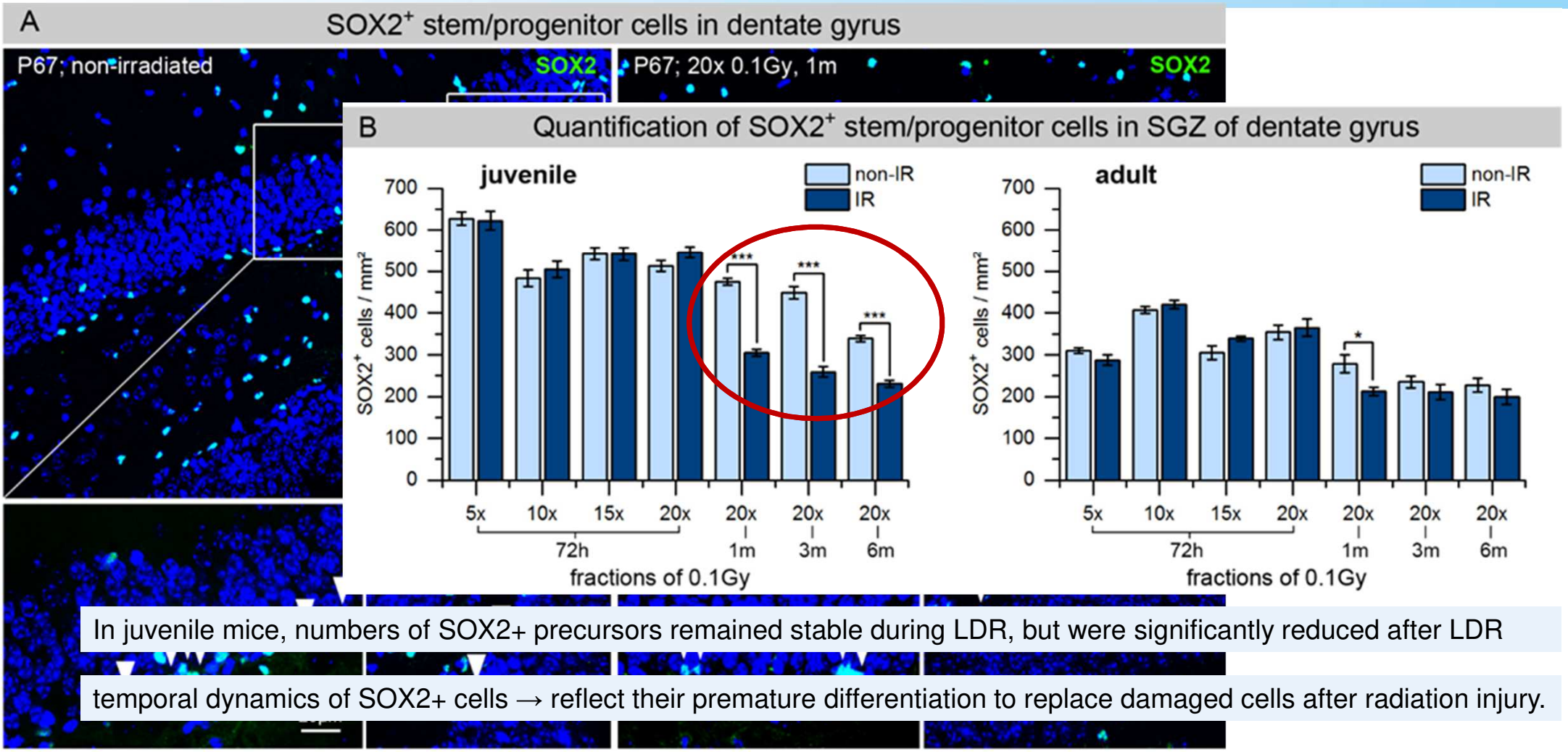
Quantification of DCX+ neuroprogenitors and their dendritic arborization



→ long-lasting effects on the number of DCX+ neurons and outgrowth and branching of their dendritic arbors

Schmal, Isermann et al. 2019

Quantification of SOX2+ stem/ progenitor cells

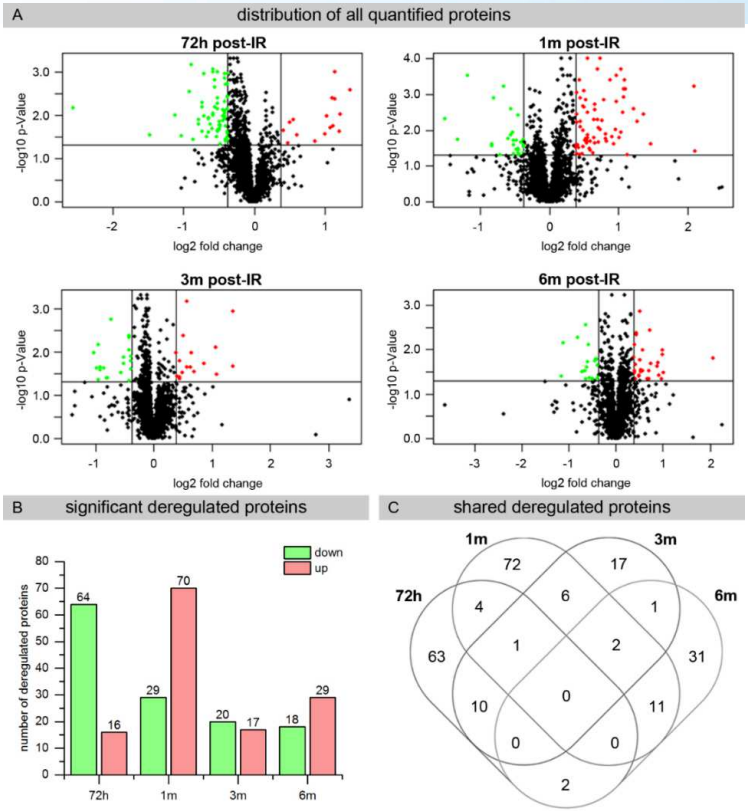


In juvenile mice, numbers of SOX2+ precursors remained stable during LDR, but were significantly reduced after LDR

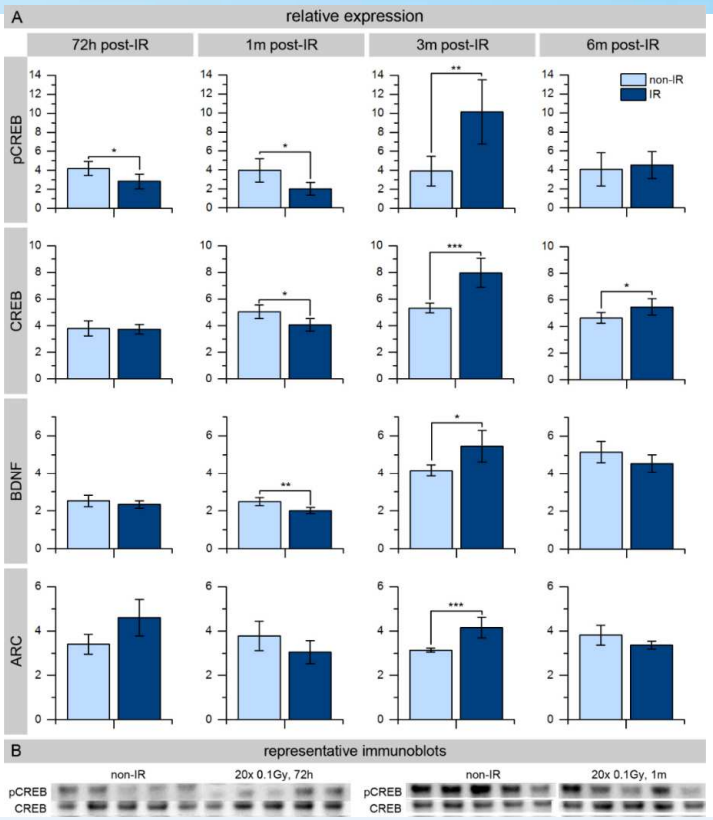
temporal dynamics of SOX2+ cells → reflect their premature differentiation to replace damaged cells after radiation injury.

Schmal, Isermann et al. 2019

Proteom analysis of juvenile hippocampus by label-free LC/MS-MS



Volcano plots → distributions of non-regulated and deregulated proteins at different time-points after fractionated LDR.
Shared proteins are presented in the Venn diagram



CREB signaling with downstream targets BDNF and ARC
→ key role in promoting neuronal survival,
neuronal proliferation, differentiation

Down-regulation of CREB-signaling directly after LDR → radiation-induced genotoxic insults suppress neurogenesis
late-term CREB-activation → stimulate neuronal cell proliferation/differentiation → promote functional regeneration

Hippocampal neurogenesis during and after fractionated LDR

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→ age-dependent decline in hippocampal neurogenesis
with most pronounced decrease in the number of neuroprogenitors

→ repeated LDR leads to persistent injury of hippocampal neurogenesis, clearly more pronounced in young mice

→ may compromise hippocampus-dependent learning and memory

DNA damage accumulation during fractionated low-dose radiation compromises hippocampal neurogenesis.
Schmal Z, Isermann A, Hladik D, von Toerne C, Tapio S, Rübe CE.
Radiother Oncol. 2019 Aug;137:45-54.

Dynamic interactions between neurons and glia cells

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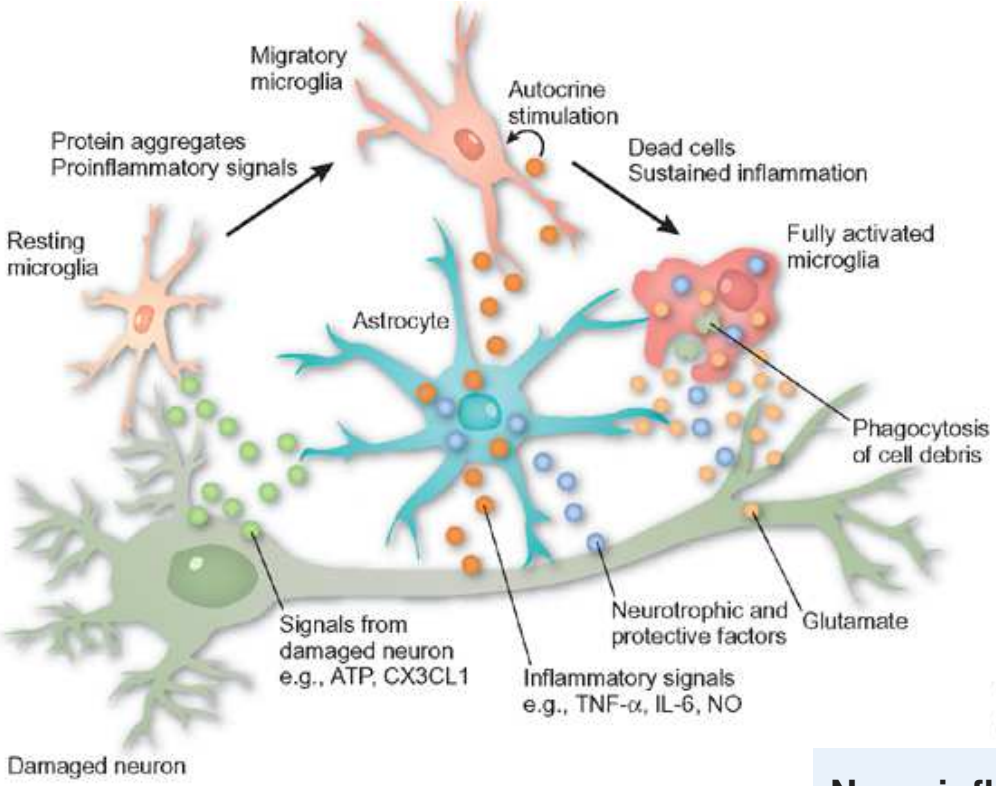
In the brain: glia cells modulate neuronal functions by supporting neuronal activity and neurotransmission



Astrocytes
→ provide neurotrophic factors to neurons
→ regulate cerebral blood flow
→ involved in repair processes following traumatic injuries

Microglia → brain-resident innate immune effector cells
→ sense tissue damage and initiate inflammatory responses

Oligodendrocytes
→ produce myelin sheath around neuronal axons

Neuroinflammation → glia cells are major mediators of neuroinflammation
→ coordinate the dynamic processes of inflammation and regeneration

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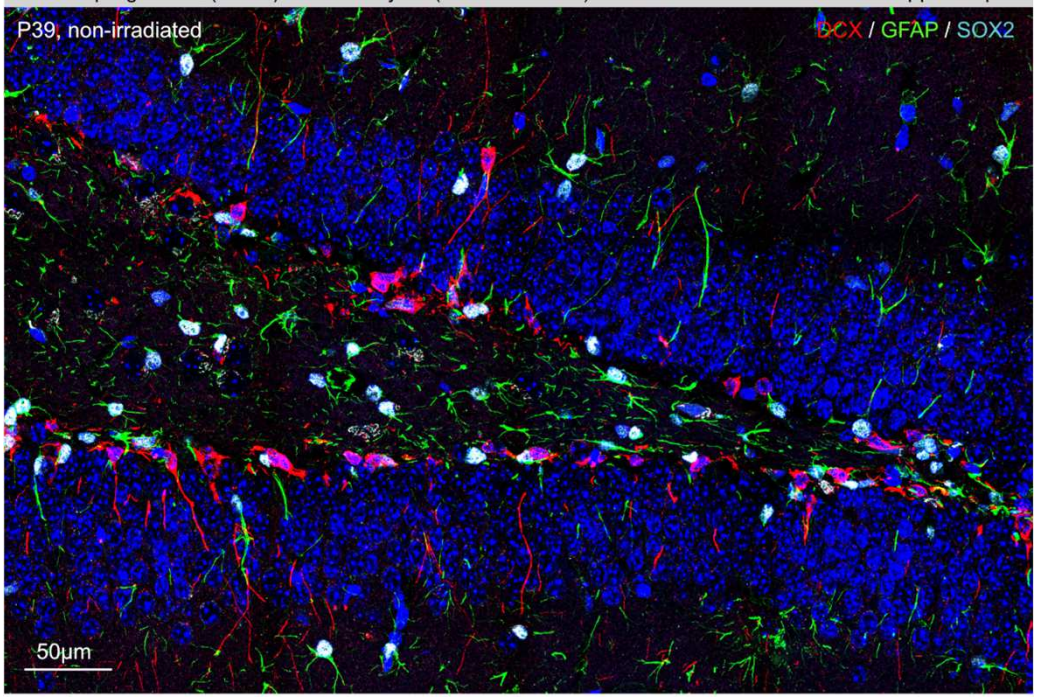
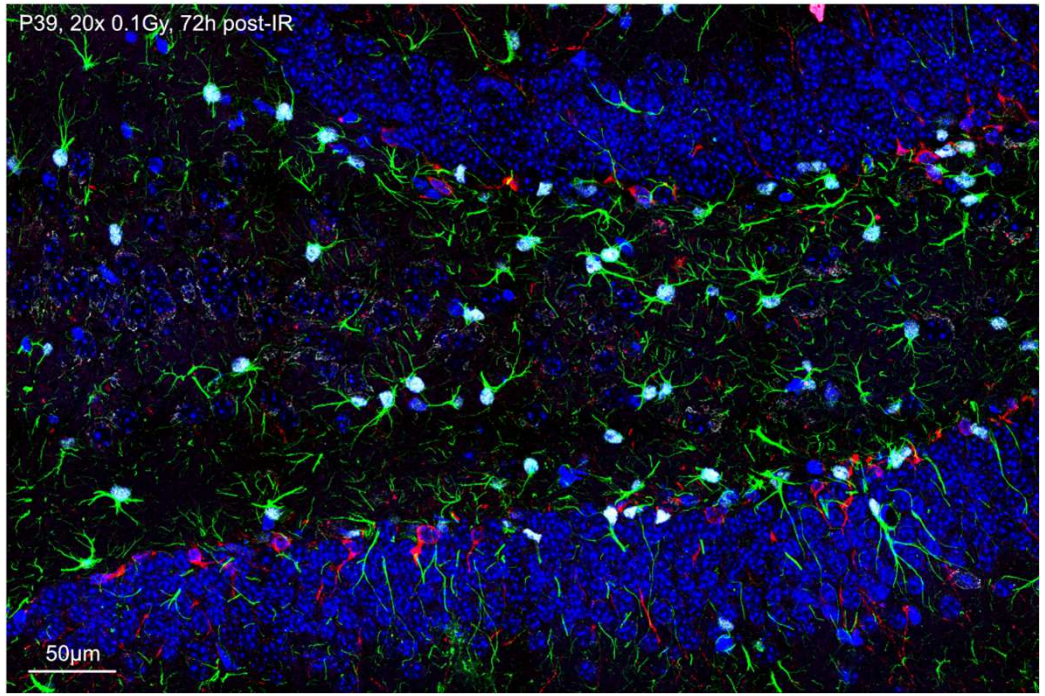
Neuroprogenitors (DCX+) and astrocytes (GFAP/SOX2+) in non-irradiated versus irradiated hippocampi

Neuroprogenitors (DCX^+) and astrocytes ($GFAP^+/SOX2^+$) in non-irradiated vs. irradiated hippocampi



Neuroprogenitors: intact dendritic arborization
with processes extending through granular cell layers

Astrocytes: normal morphologies

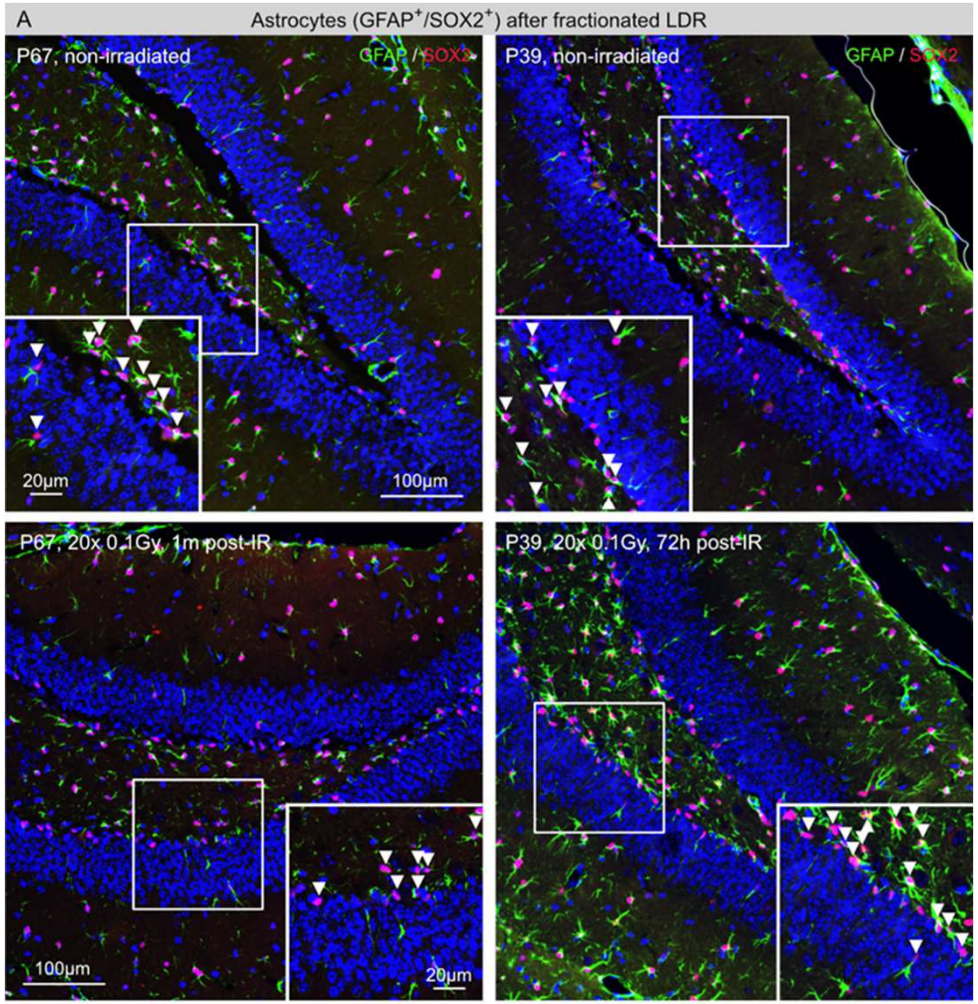


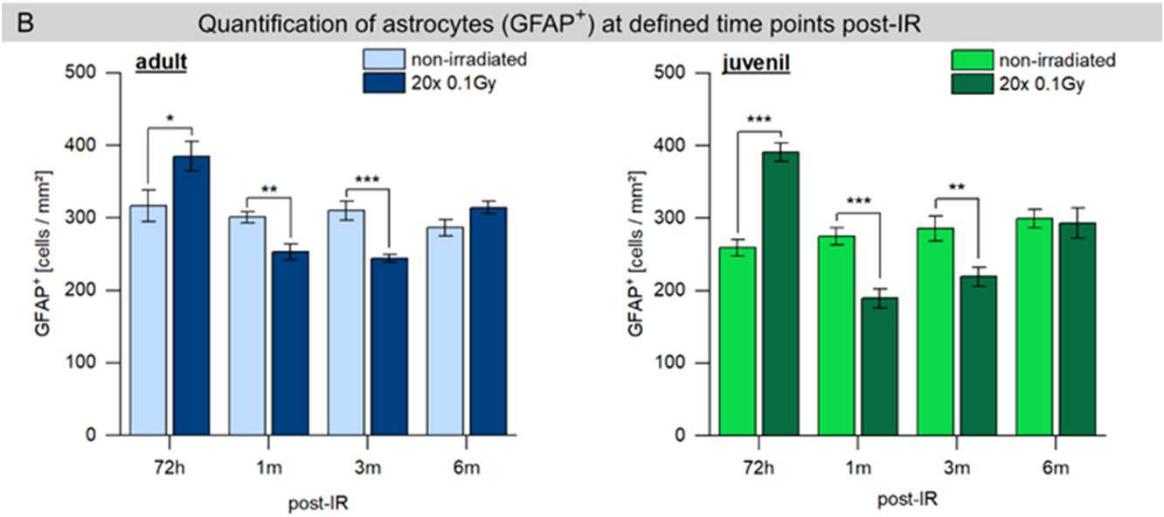
Neuroprogenitors: reduced dendritic arborization

Astrocytes: altered, hypertrophied morphologies
(increased cell body size, extensive branching of GFAP-positive processes)

Schmal, Hammer et al. 2021

Astrocytes after fractionated LDR





Quantification of astrocytes after fractionated LDR

→ initial up-regulation (72h post-IR)

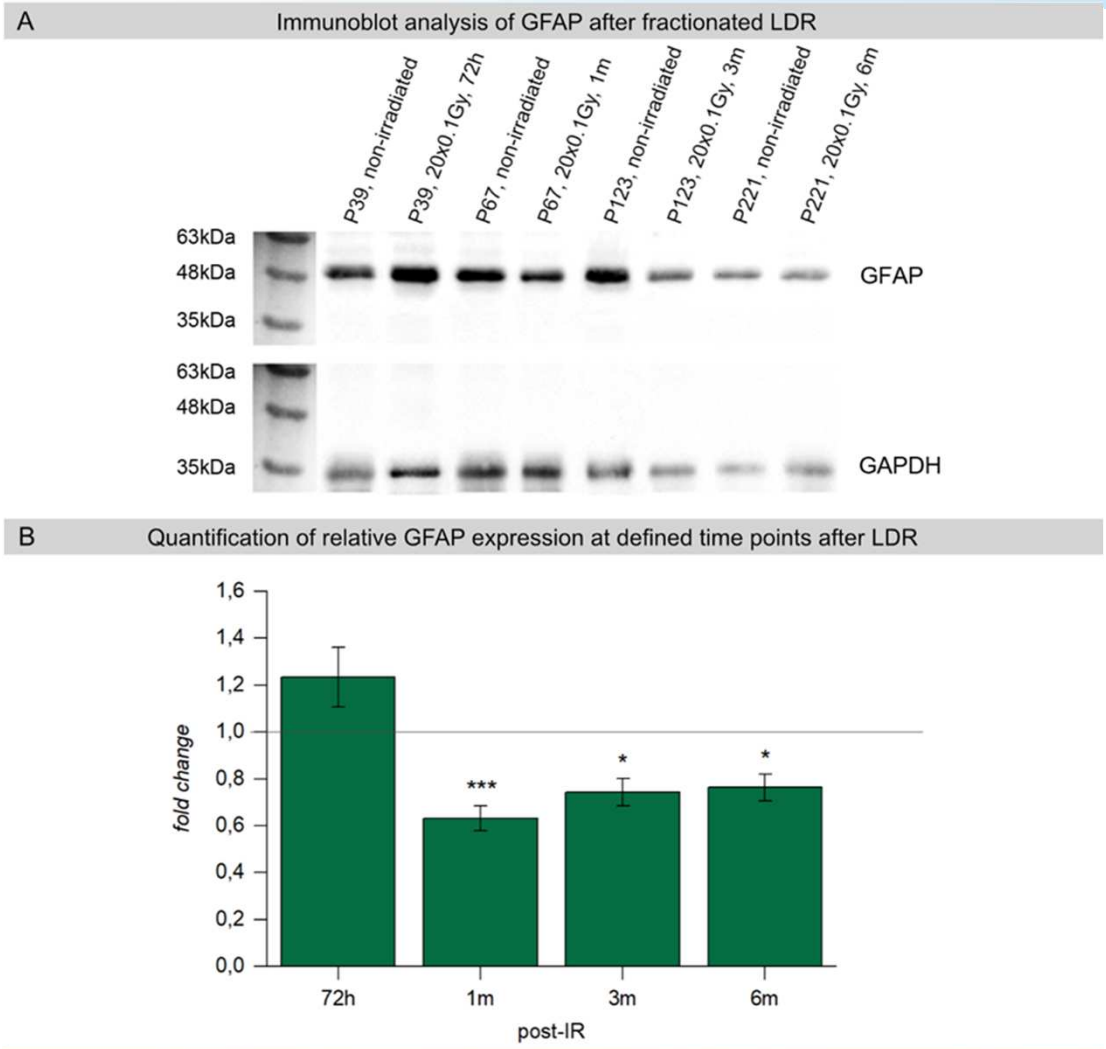
→ subsequent down-regulation (1m and 3m post-IR)

→ normalization at 6m post-IR

→ radiation-induced effects more pronounced in juvenile hippocampi

Schmal, Hammer et al. 2021

Astrocytes after fractionated LDR: GFAP protein expression



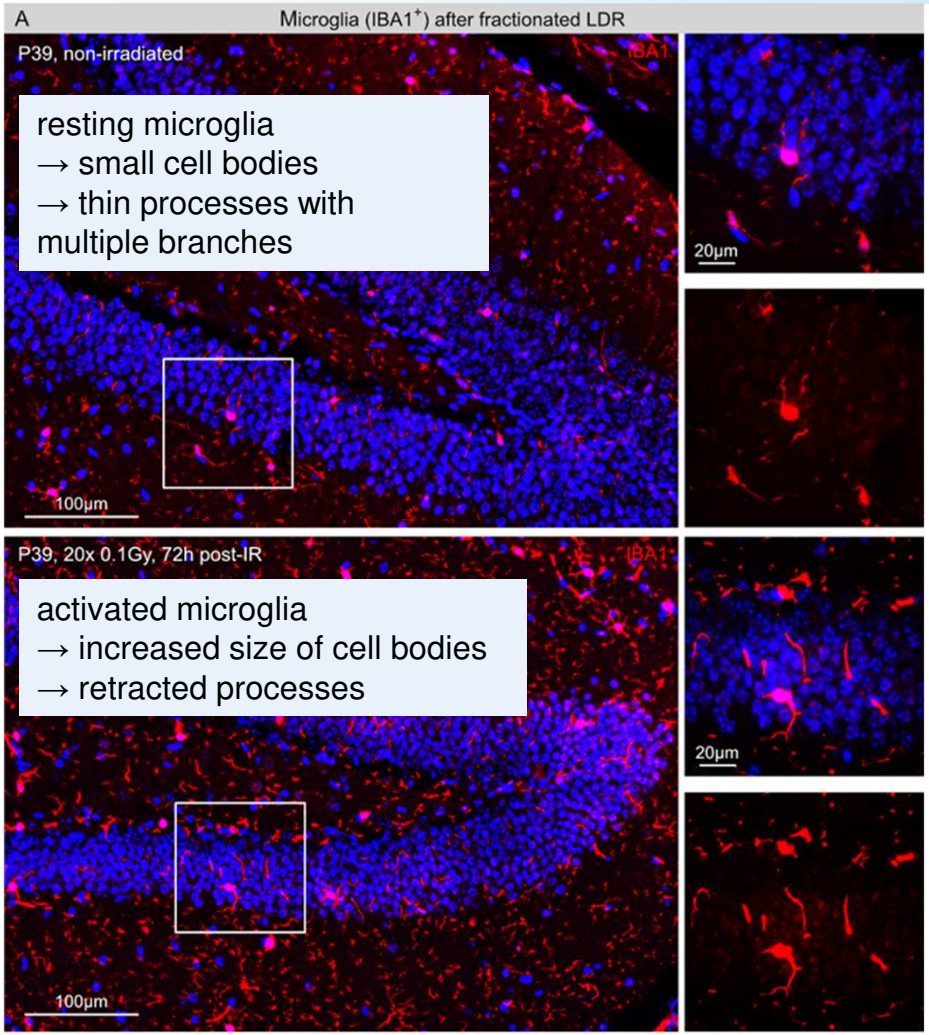
Reactive astrocytes generally increase the production of *glial fibrillary acidic protein* (GFAP)

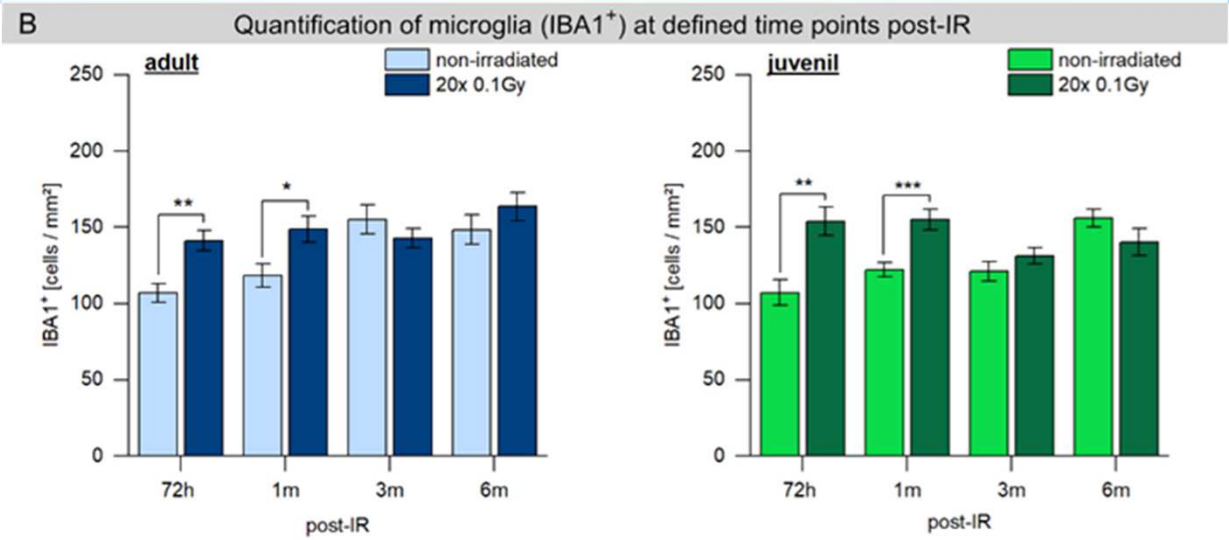
GFAP immunoblotting
→ radiation-induced variations GFAP protein expression:
→ acute increase at 72h post-IR,
→ significant decline at 1m and 3m post-IR.

→ chronic stress-induced atrophy of astrocytes with decreased GFAP expression.

Schmal, Hammer et al. 2021

Microglia after fractionated LDR





Following fractionated LDR

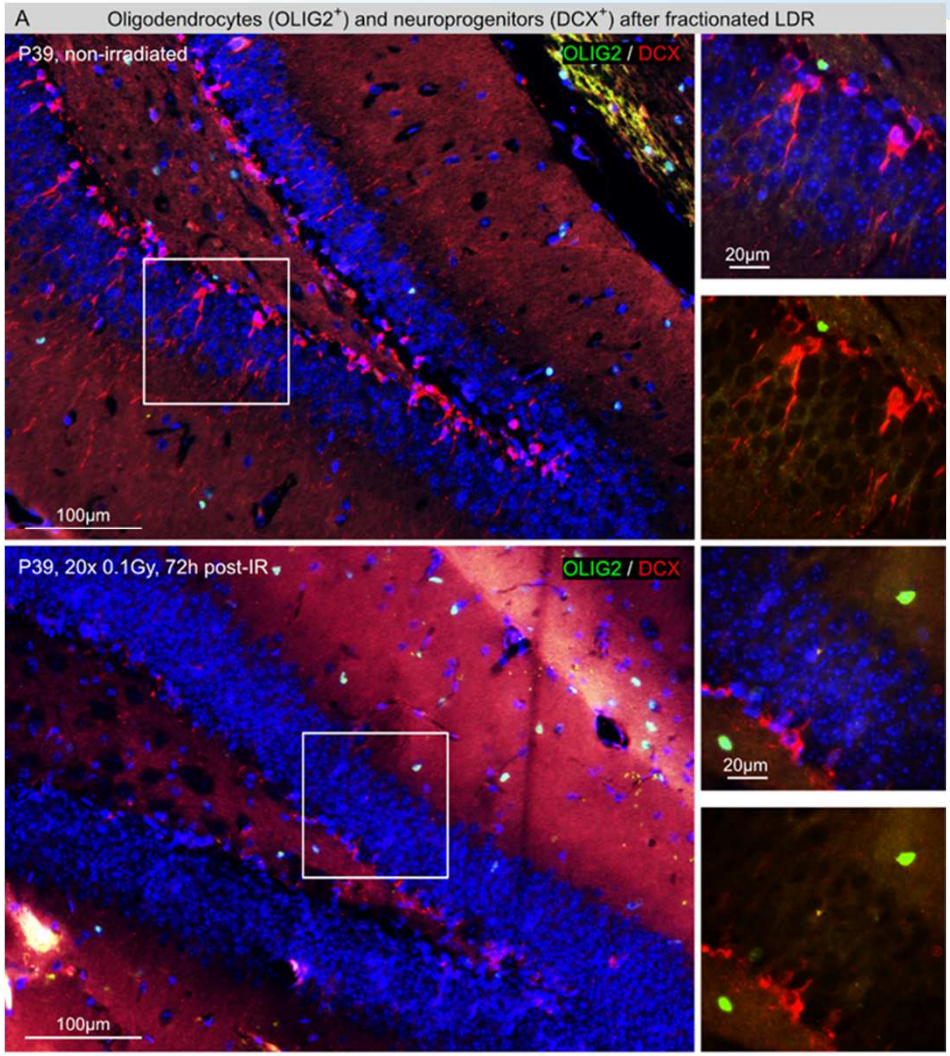
microglia numbers significantly elevated at 72h and 1m post-IR

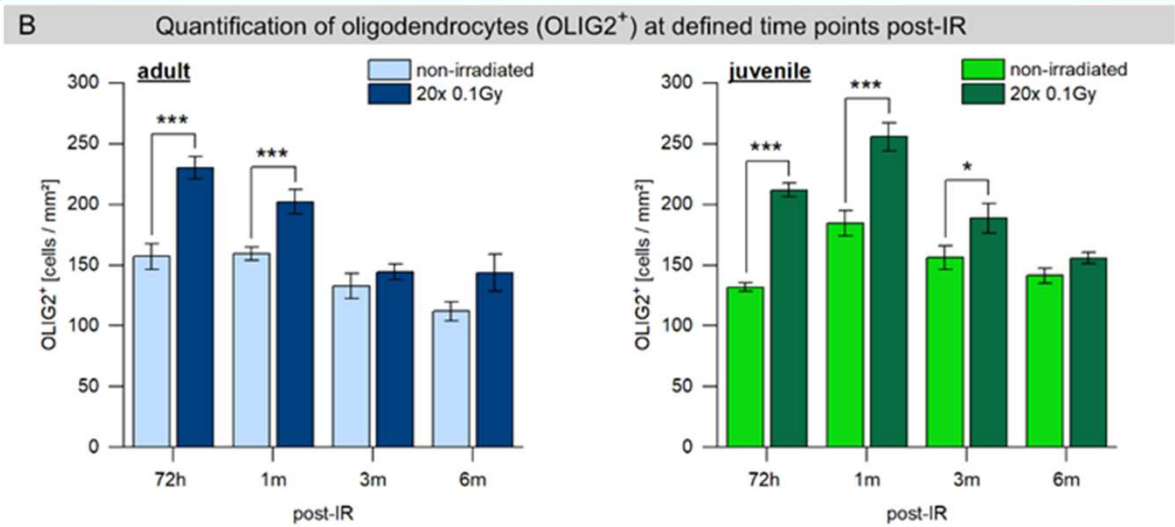
After radiation-induced injury

→ microglia remove cell debris of damaged neuroprogenitors

Schmal, Hammer et al. 2021

Oligodendrocytes after fractionated LDR



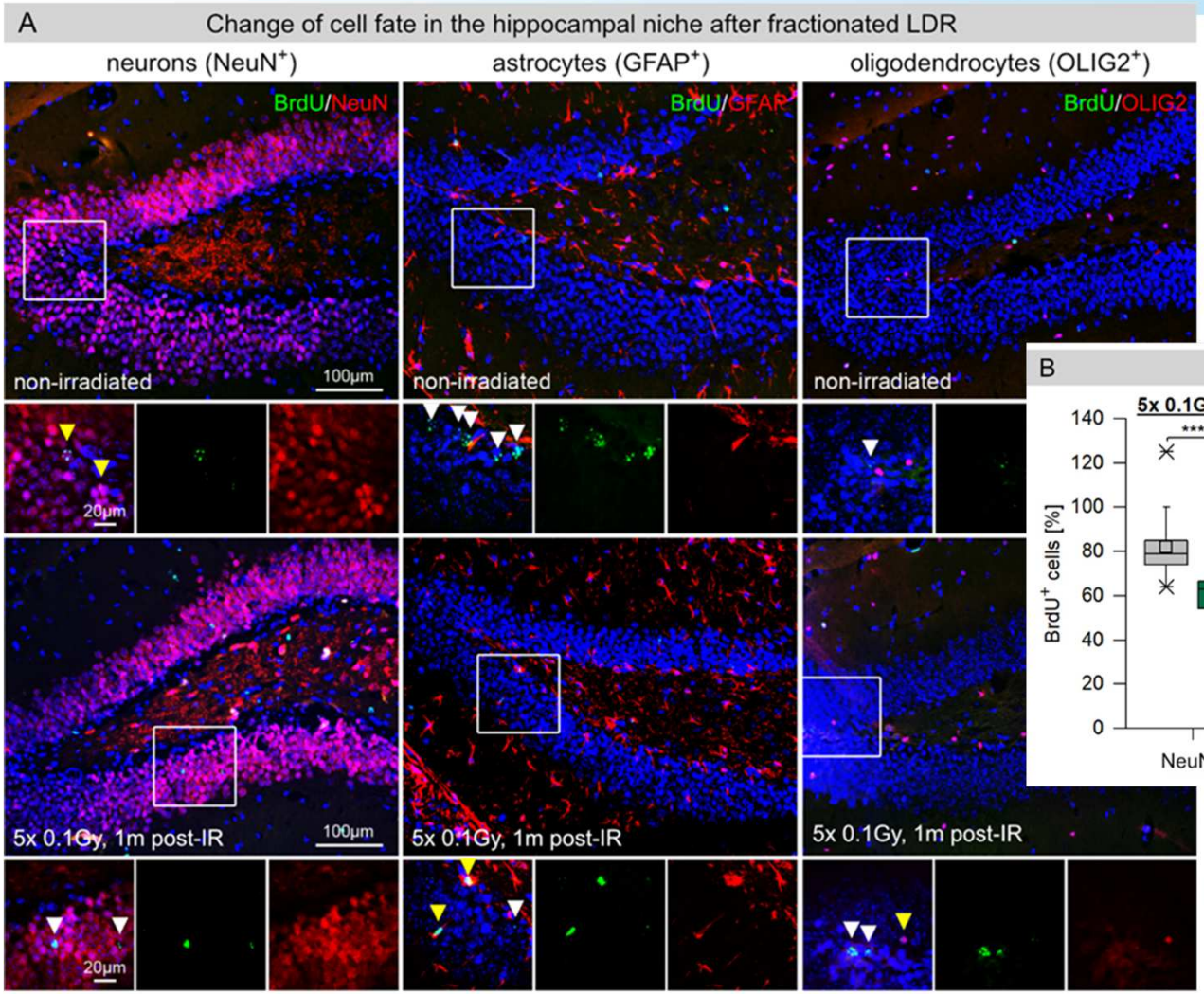


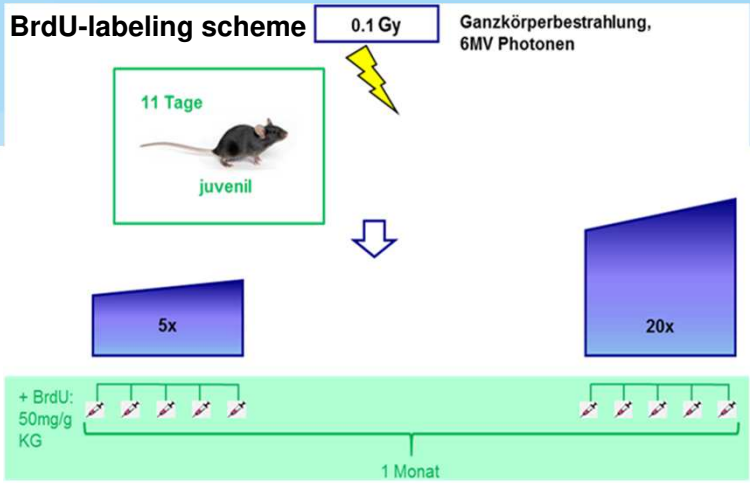
→ significantly increased numbers of oligodendrocytes at 72h and 1m post-IR

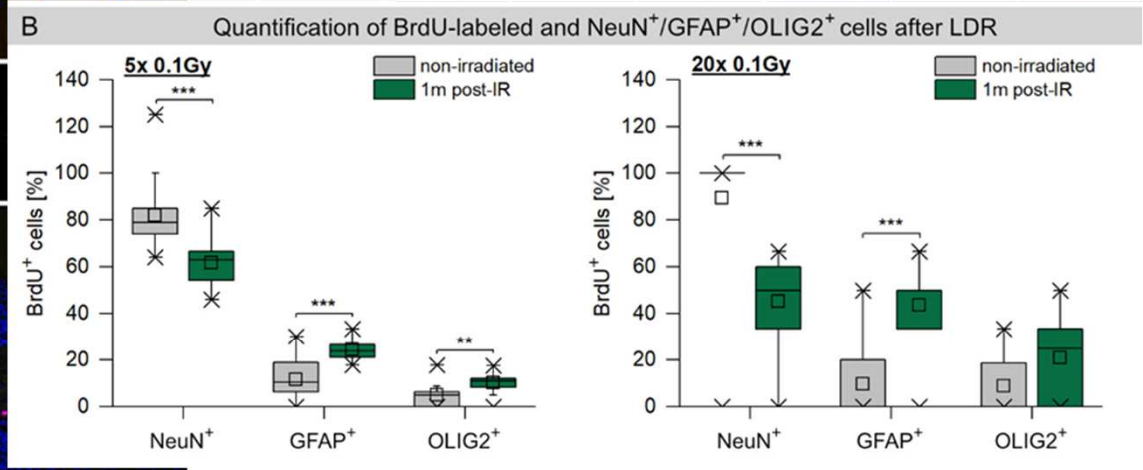
→ oligodendrocytes support myelin maintenance and repair after radiation-induced neuronal damage

Schmal, Hammer et al. 2021

Change of cell fate in the hippocampal niche after fractionated LDR







→ impressive shift in cell-fate determination from neurogenesis to gliogenesis

Schmal, Hammer et al. 2021

MRI study: in-vivo imaging of the brain after fractionated LDR

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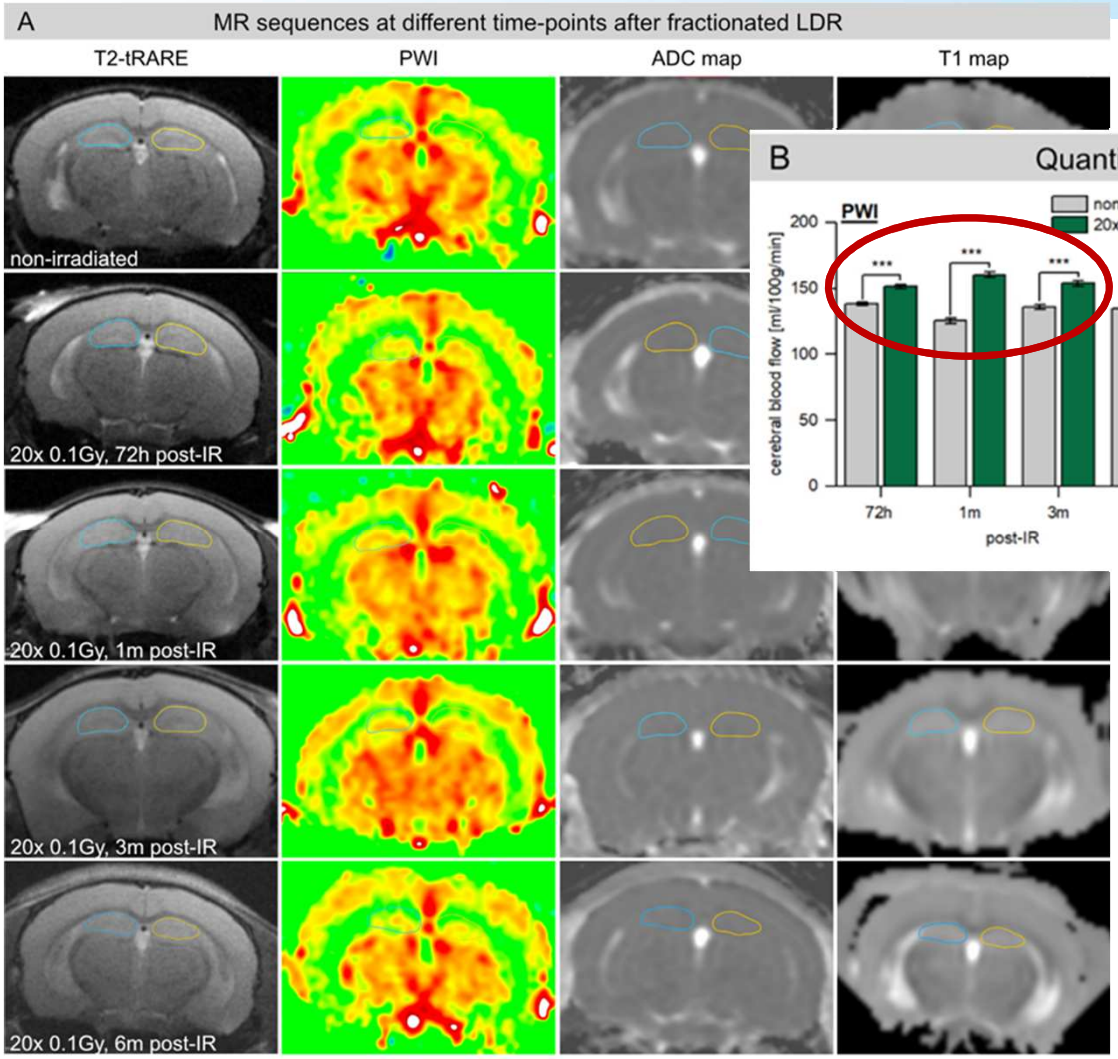
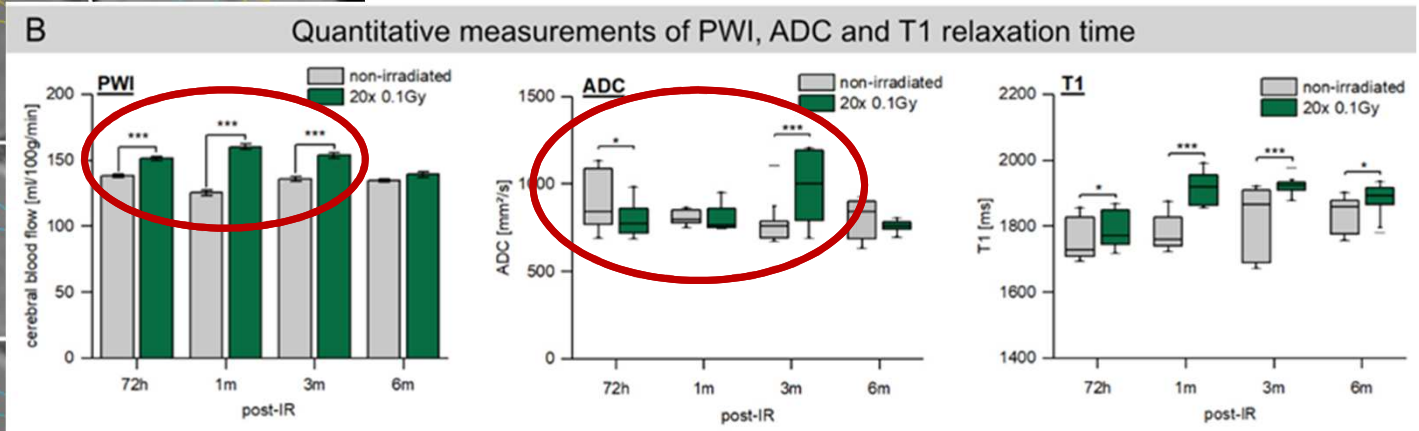




→ elevated blood flow after fractionated LDR (PWI)

→ intracellular swelling → interstitial edema (ADC)

functional imaging with appropriate MRI protocols
→ sensitive enough to assess alterations in vascular reactivity associated with radiation-induced inflammatory response

Schmal, Hammer et al. 2021

Conclusions

Preclinical mouse model of fractionated LDR
→ even low doses induce long-lasting inflammatory responses in the hippocampal region,
with local increases of activated microglia, reactive astrocytes and myelinating oligodendrocytes

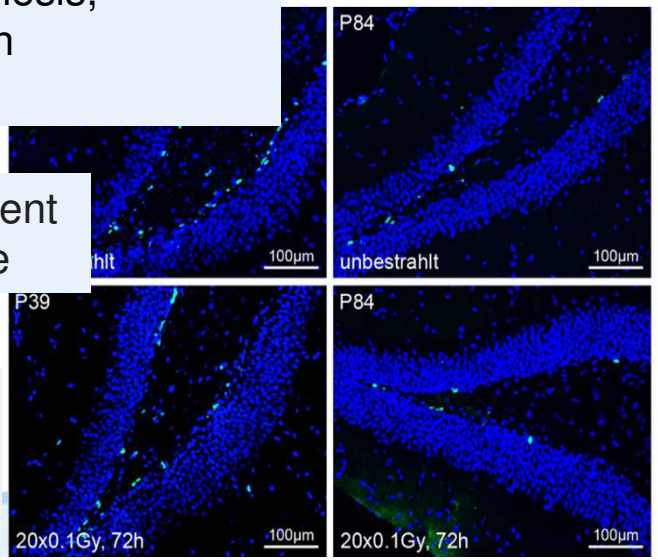
Glial activation with subsequent release of pro-inflammatory mediators increased local blood circulation and vascular permeability, as supported by functional MRI analysis.

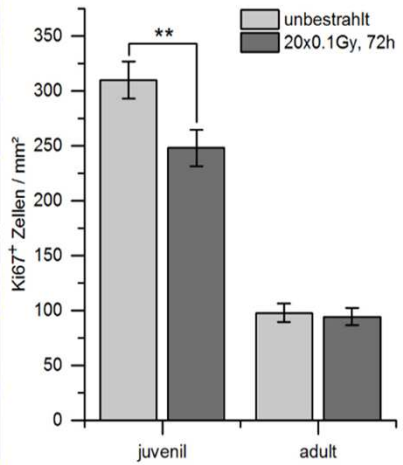
radiation-induced inflammatory reaction → associated with the deterioration of neuronal progenitors

Higher numbers of stem/ progenitor cells in the developing brain
→ enhance inherent vulnerability of hippocampal neurogenesis,
→ explain enhanced inflammatory reaction in juvenile brain
due to more pronounced neuronal damage

→ radiation-induced injury to the neural stem cell compartment may contribute to the development of neurocognitive decline

Schmal, Hammer et al. 2021





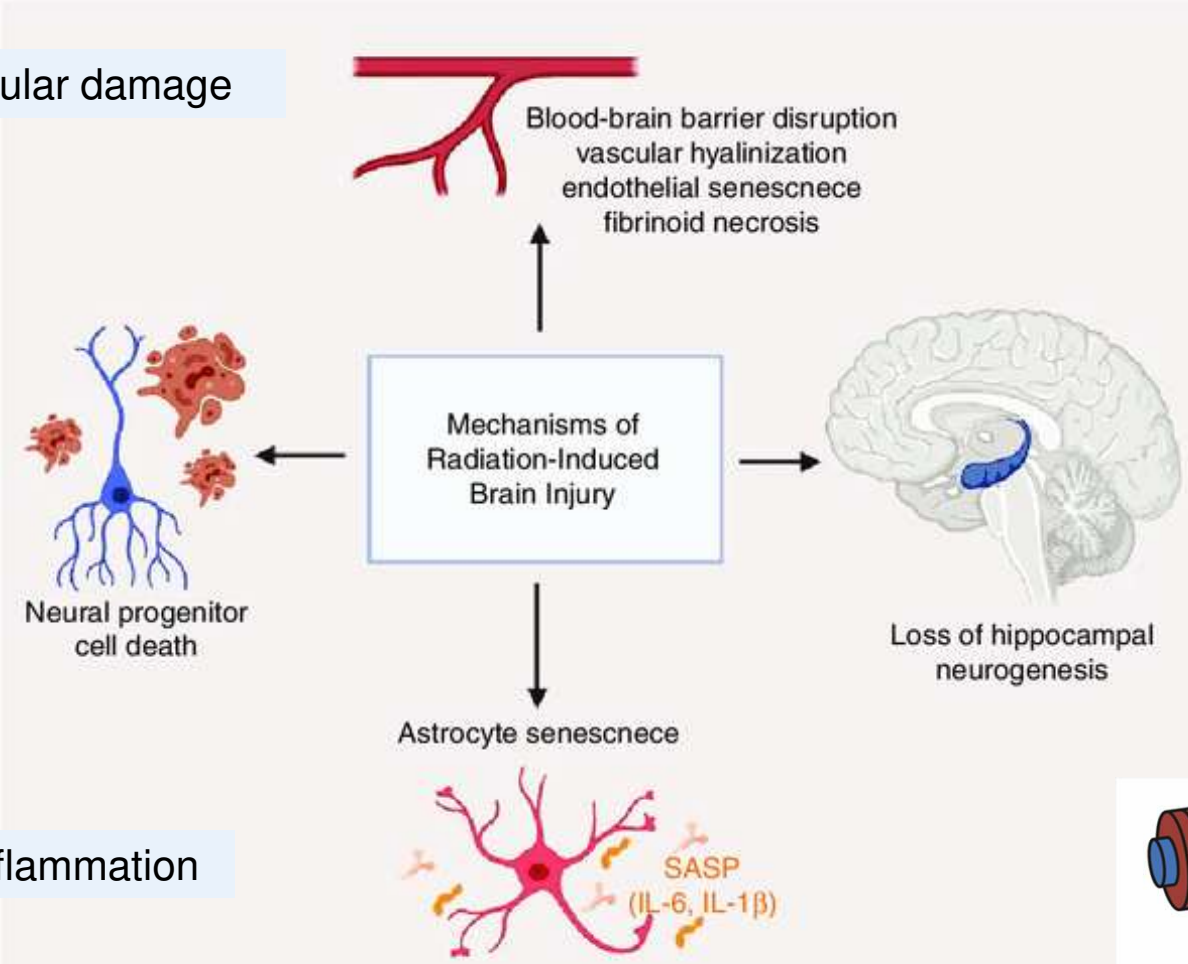
Fractionated Low-Dose Radiation Induces Long-Lasting Inflammatory Responses in the Hippocampal Stem Cell Niche.
Schmal Z, Hammer B, Müller A, Rübe CE.
Int J Radiat Oncol Biol Phys. 2021 Dec 1;111(5):1262-1275.

Pathomechanisms of radiation-induced brain injury

radiation-induced neurovascular damage

age-dependent effects of IR exposure on hippocampal neurogenesis

radiation-induced neuroinflammation



→ multiple other factors are implicated in the aetiology of radiation-induced brain injury

Thank you for your attention !

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