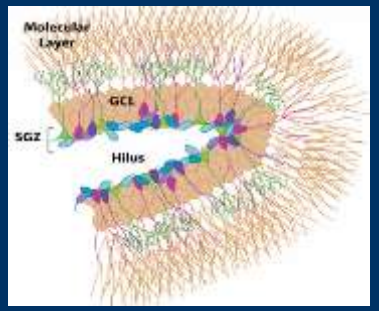
Neurocognitive effects after radiation exposure of children



Simonetta Pazzaglia, Laboratorio di Tecnologie Biomediche (TEB), ENEA, Rome, Italy

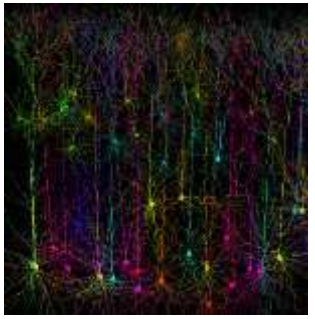
EU Scientific Seminar/Webinar 2020 on *"Radiosensitivity" of children - Health issues after radiation exposure at young age*

1st December 2020

Introduction

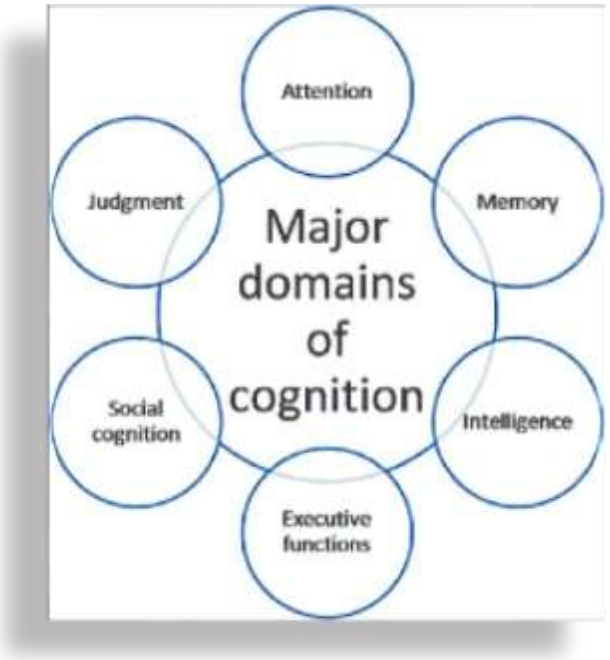
Brain development begins well before birth and continues through the early adult years. The biology of this process is influenced by (i) the genes that are passed on from the parents to the child, (ii) by the environment of the mother's womb, and (iii) by the world the child experiences during infancy and childhood.

Environmental stressors, including **ionizing radiations,** have the capacity to disrupt the development of all of the body's organ systems. The nature and severity of that disruption depend on the level and duration of exposure, and most importantly, on the timing during the developmental process. Early insults can lead to a broad range of lifelong problems in both physical and mental.



When it is relatively immature, the brain is particularly susceptible to adverse impacts on the formation of its basic circuits. This may result in permanent impairment, thereby leading to a wide range of lifelong, adverse impacts on learning, behavior, and health that **impose devastating human and financial costs**.

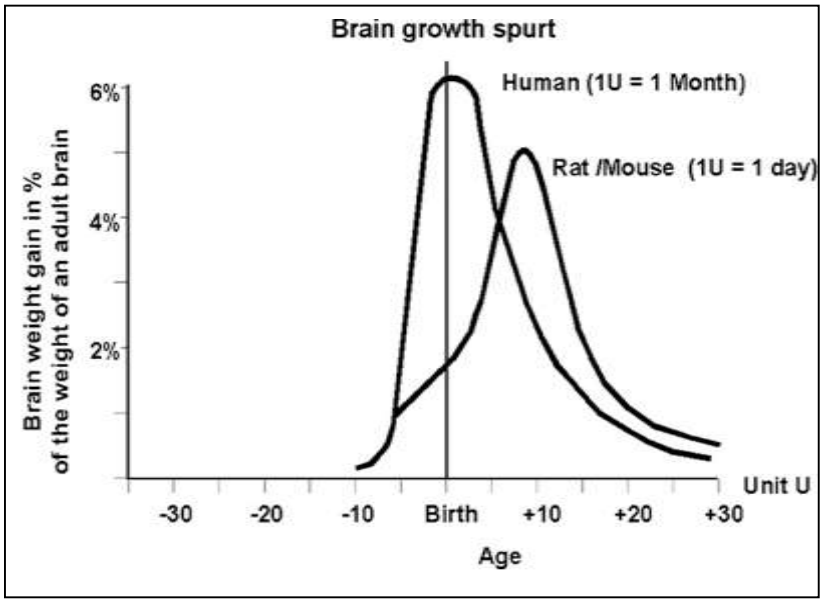
Cognitive development



- Cognitive functions start to develop in utero, continue until young adulthood, and start to decline at older ages
- Cognition is a set of functions ensuring the ability to think, learn, reason, image and remember
- Behind genetic factors, environmental agents - including **ionizing radiations** - influence and detemine the trajectory of cognitive development and decline

Brain growth spurts in human and mice

During development the brain experience a marked growth in size indicated as **brain growth spurt**



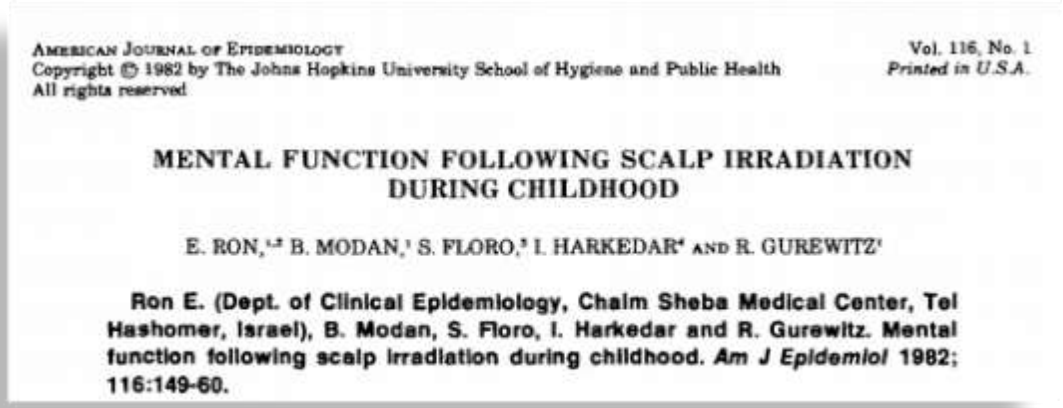
DOI:10.1016/j.eplepsyres.2009.09.019

This is expressed as curves of **brain weight gain as a percentage of the adult brain weight,** as a function of age. The units of time for humans are months and for rats/mouse days. It peaks around birth in humans and postnatal day 10 in mice.

This period corresponds to high sensitivity to toxicant exposure, with neurotoxic manifestation in the adult mice (Eriksson et al., 2000).

The developing brain is exposed to ionizing radiation in a number of clinical situations related to medical diagnostics and therapy

First evidence



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MENTAL FUNCTION FOLLOWING SCALP IRRADIATION DURING CHILDHOOD

E. RON,[1,2] B. MODAN,[1] S. FLORO,[3] I. HARKEDAR[4] AND R. GUREWITZ[1]

Ron E. (Dept. of Clinical Epidemiology, Chaim Sheba Medical Center, Tel Hashomer, Israel), B. Modan, S. Floro, I. Harkedar and R. Gurewitz. Mental function following scalp irradiation during childhood. *Am J Epidemiol* 1982; 116:149-60.

The detrimental effects of ionizing radiation on cognition have been known for some time, since **1982**

Background

Between 1950 and 1960 about 20,000 **Israeli children** were treated for **tinea capitis** by **x-ray** to eradicate the disease. Dosimetry determined that these children were subjected to a mean brain **dose of 130 rads**. **Almost 20 years later**, **radiation effects on the CNS were evaluated in about 11,000 of the Irradiated children** and in two non irradiated, tinea-free comparison groups: (a) ethnic, sex- and age-matched individuals from the general population, and (b) siblings.

Results

While not all comparisons were statistically significant, there was a consistent trend for the irradiated subjects to exhibit more often signs of central nervous system impairment compared to either unexposed group. **The irradiated children had** (i) **lower examination scores on scholastic aptitude**, (ii) **intelligence quotient** (IQ) and (iii) **psychologic tests**, (iv) **completed fewer school grades**, and (v) **had an increased risk for mental hospital admissions** for certain disease categories. A slightly higher frequency of mental retardation was also suggested.

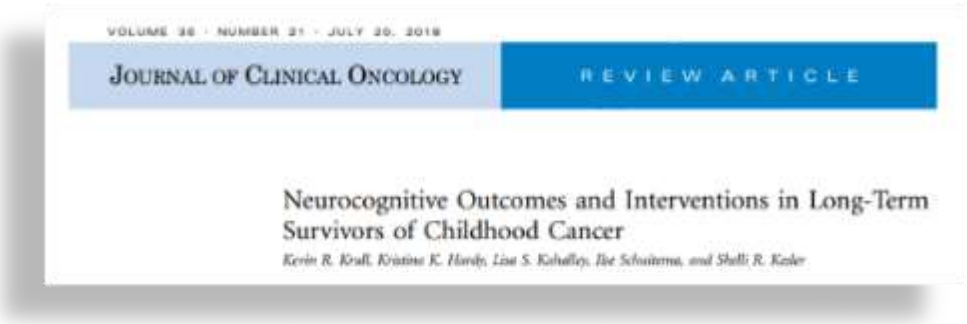
Conclusion

These effects lead the authors to conclude that radiation to the immature brain may cause damage to the central nervous system.

Other evidences

Brain Tumor Survivors are at risk for cognitive deficit and cranial radiotherapy is now a well-recognised risk-factor for cognitive impairment

After ratiotherapy of CNS cancers, young age survivors have poor neurocognitive outcome. They may develop, motor, intellectual, visual, and psycoemotional dysfunctions, with moderate to severe disabilites. Younger age at diagnosis, higher cranial irradiation dose, larger brain volume irradiated, and longer time since treatment are risk factors for worse neurocognitive outcomes.


VOLUME 36 · NUMBER 21 · JULY 20, 2018

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Neurocognitive Outcomes and Interventions in Long-Term Survivors of Childhood Cancer

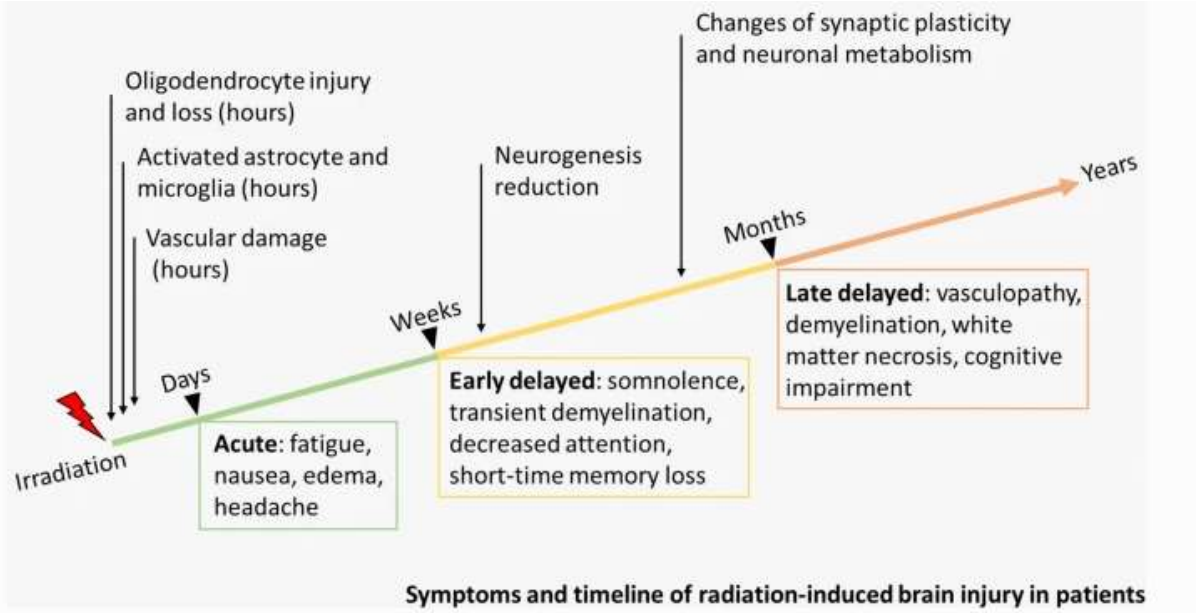
Kevin R. Krull, Kristine K. Hardy, Lisa S. Kahalley, Ilse Schuitema, and Shelli R. Kesler

Neurocognitive problems are also commonly experienced by survivors of acute lymphoblastic leukemia (ALL) treated with CNS prophylaxis.

Cranial radiation carries particular risk to memory function, especially the process of forming new memories of events or facts that is subserved by the hippocampus in the medial temporal lobe

Time-line of radiatio therapy-induced brain injury

Radiation-induced progressive injuries bto the CNS



Radiation-induced early injury to the CNS which becomes chronic, leading to a progressive and irreversible cognitive decline

Chu, C. *et al. tem Cell Rev and Rep* **16,** 639–649 (2020).

Traditionally, radiation-induced brain-injury is classified into **Acute**, **Early** and **Late** delayed based on time between radiotherapy and the onset of side-effects. While acute and early delayed effects are generally transient, **cognitive decline** may become **manifest many months to years after irradiation** and get progressively worse.

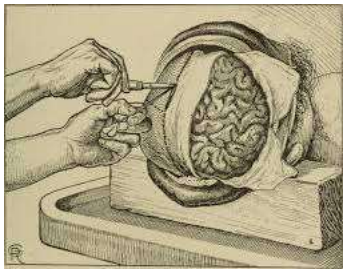
Cognitive decline in the clinical setting

The frequency of radiation-induced cognitive impairment varies among studies and it is influenced by a number of factors including:

- Patient age at exposure
- Age at cognitive assessment,
- Definition of neurocognitive impairment
- Tumor type
- Disease progression
- Radiotherapy modality (WBRT, PBRT, stereotactic)
- Radiation dose
- Use of multimodal treatments, including concurrent chemoterapy and surgical procedures

Therefore, although cognitive dysfunction significantly affect the quality of life in pediatric patients that underwent radiation therapy, determining and comparing the frequency of cognitive decline in the clinical setting remain challanging.

Technical obstacles and limited ability to access human samples



Studying human brain tissues is hampered by several potential technical obstacles

- Standardization of essential methodological requirements would be needed, e.g., the maximum premortem agonal period, maximum time elapsed from death to tissue fixation and fixation times.
- The ability to access human samples by establishing brain-tissue bank/s from large patient cohorts open to researchers should be facilitated
- Open data repositories of human neurogenomics should be organized

Moving from association studies towards mechanistic studies to elucidate pathogenesis of radiation-induced cognitive impairment required animal models

Animal models

Understanding of the factors modulating brain radiation response may be of help to minimize the risk of adverse effects and towards the identification of early prevention measures against radiation-dependent **adverse effects**

Experimental animal model may shed light on the factors influencing brain radiation response

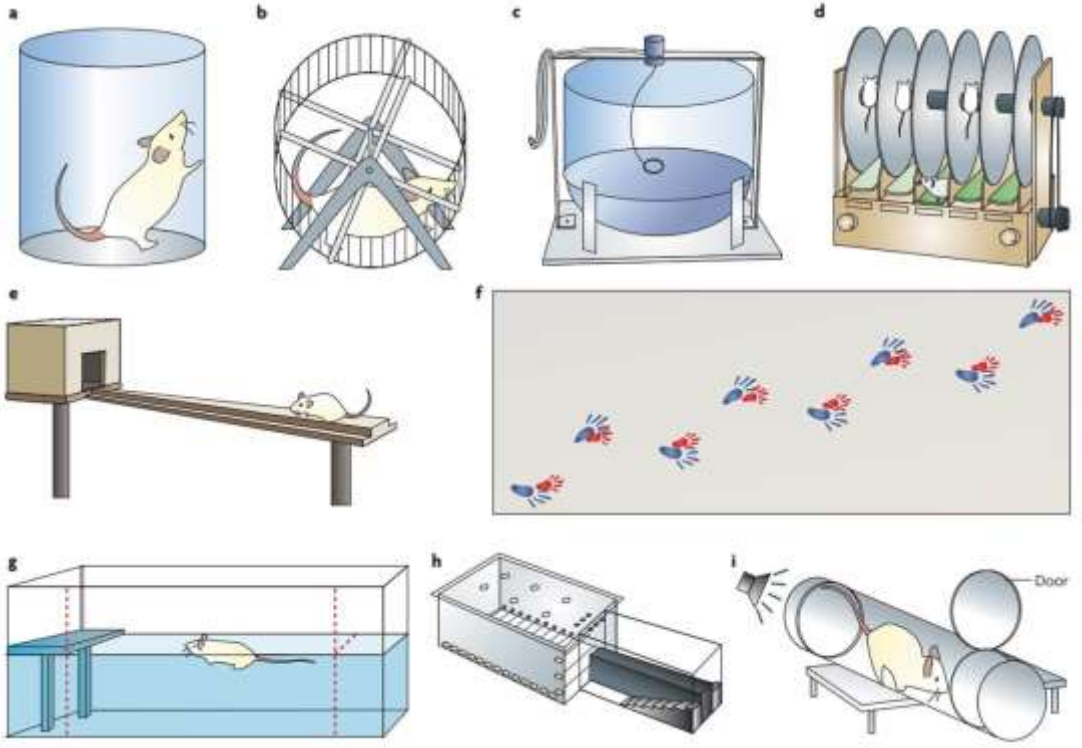
- ✓ age at exposure, characterization of vulnerable periods
- ✓ genetic backgrounds-dependence of radiation-induced effects
- ✓ combined effects of ionizing radiations and other environmental/chemical factors

Also improving the mechanistic understanding of radiation-induced cognitive effects

Radiation-induced impairment of cognitive function in rodents

Radiation-induced impairment of cognitive function and memory may also be detected in rodents and behavioral tests are considered the best avalable strategy to uncover brain functions in animal experiments

The use of one test is not ideal and a number of **behavioral tests** have been developed to **detect and quantify** the presence of motor and memory impairments in **rodent models**.

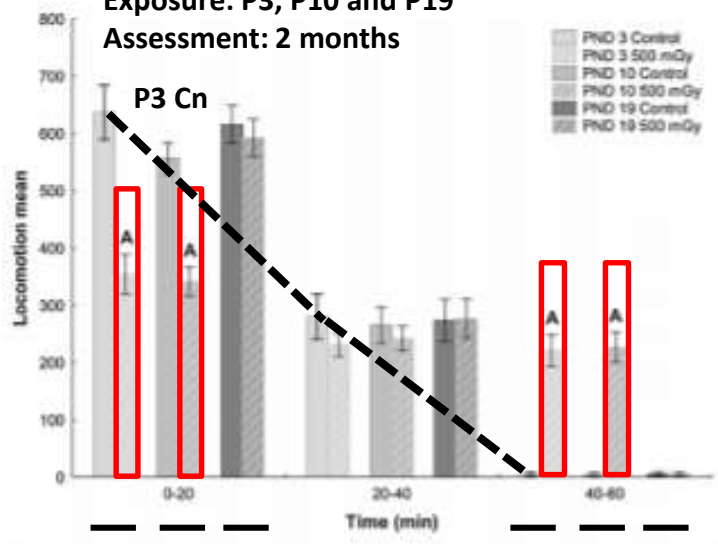


Radiation-induced changes in spontaneous behaviour in a novel home environment

Normal adaptation to a novel home environment consists in high activity during the first 20 min and a low activity at the end of the 60 min observational period.

Critical age-window of susceptibility

Radiation dose: 500 mGy
Exposure: P3, P10 and P19
Assessment: 2 months



Hypoactivity ⟷ **Hyperactivity**

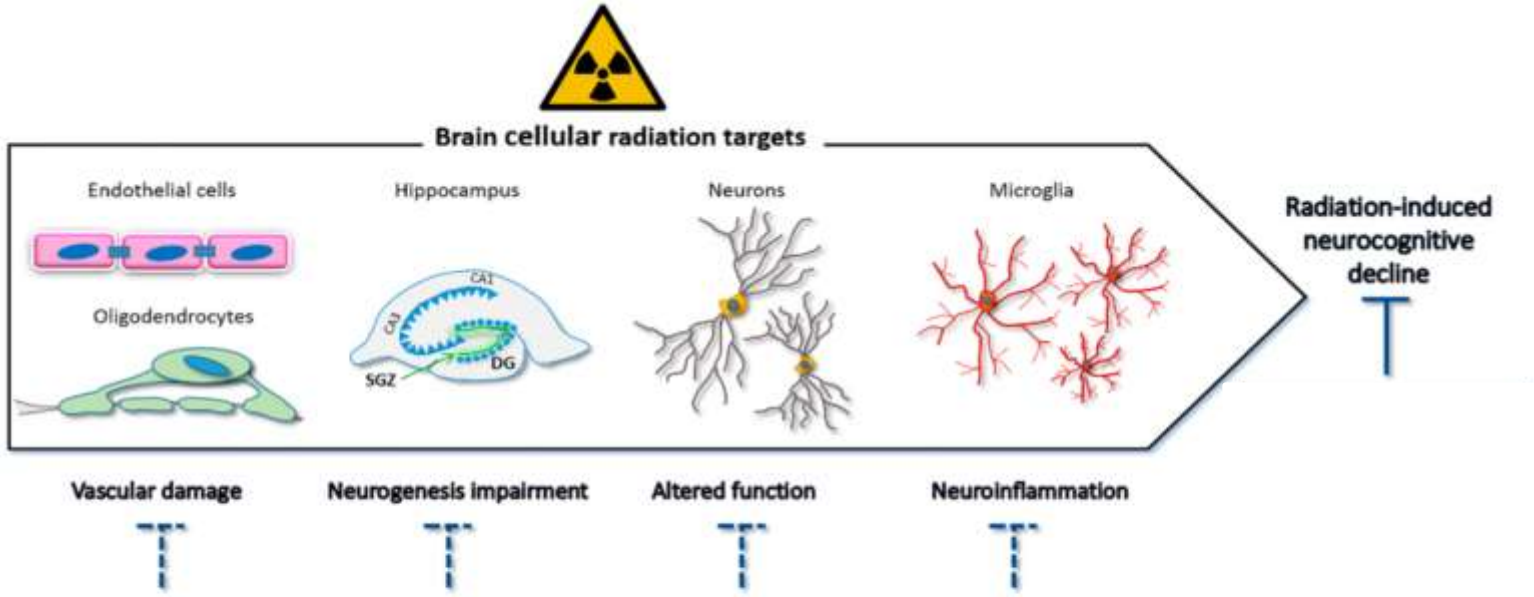
Lack of habituation and cognitive dysfunction

P3 and P10 represent a critical age windows for induction of developmental radiation-induced neurotoxicity

Eriksson P, et al. Behav Brain Res. 2016 May 1;304:11-9.

Mechanisms of radiation-induced brain injury

Brain radiation injury is multifactorial and complex, involving dynamic interactions between multiple cell types

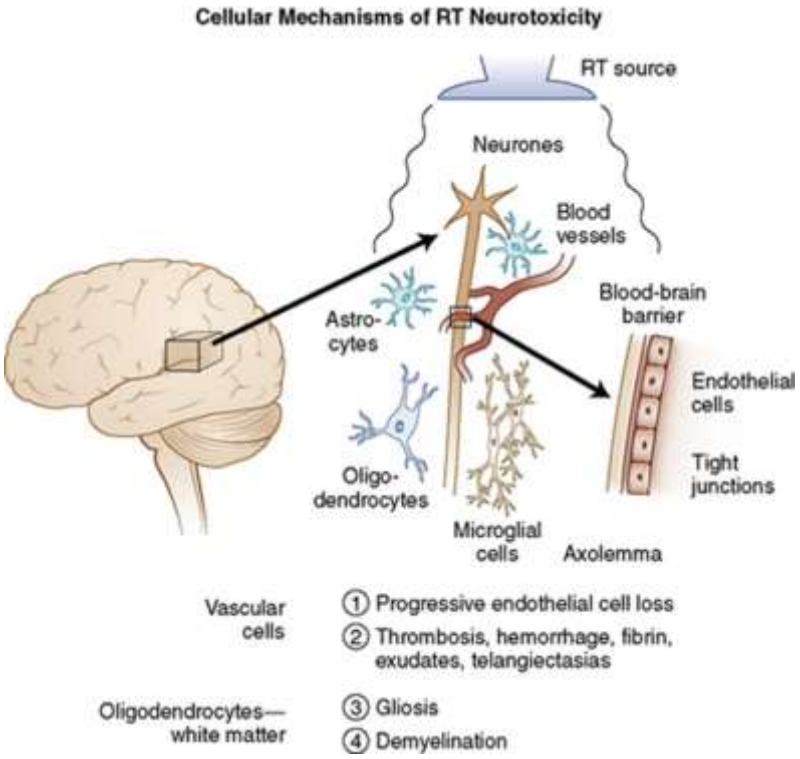


Potential mechanisms triggering radiation-induced cognitive impairment are:

- vascular damage (BBB Disruption),
- decline in oligodendrocytes and other glial cells,
- neuroinflammation caused by activated microglia,
- impaired hippocampal neurogenesis,
- altered function of adult neurons.

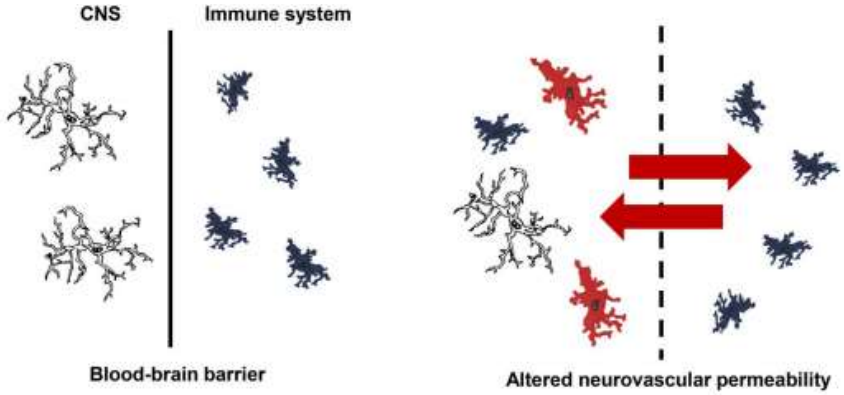
All these alterations, thought to occur concomitantly, are likely contribute to the development of radiation-induced cognitive impairment

Vascular damage and decline in oligodendrocytes and other glial cells



Vascular Damage

The blood–brain barrier (BBB) is a highly selective semipermeable border of endothelial cells that restrict the passage of most soluble molecules, from the systemic circulation, into the CNS. The BBB is composed of endothelial cells, pericytes, and astrocyte end-feet that form tight junctions. Irradiation can impair the integrity of the BBB altering neurovascular permeability and allowing inflammatory cells to enter the brain and propel neuroinflammation.

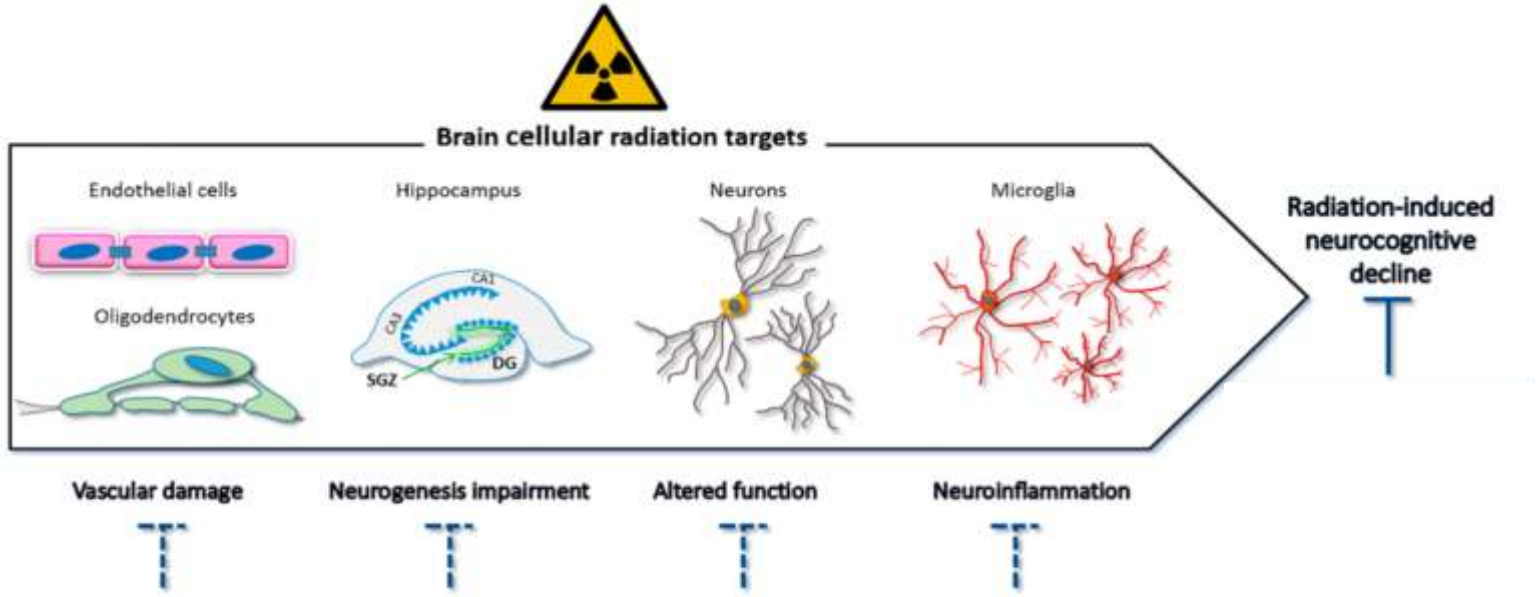


Oligodendrocytes

The mechanisms of neurotoxicity from radiation therapy include demyelination. Oligodendrocytes are responsible for the myelin production in the CNS. Irradiation of CNS induces depletion of oligodendrocytes and suppresses, at least transiently, the production of oligodendrocyte progenitors.

Mechanisms of radiation-induced brain injury

Brain radiation injury is multifactorial and complex, involving dynamic interactions between multiple cell types

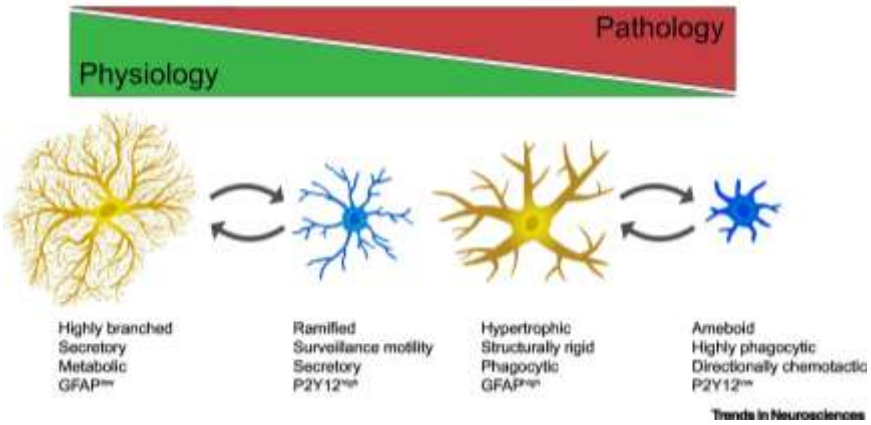


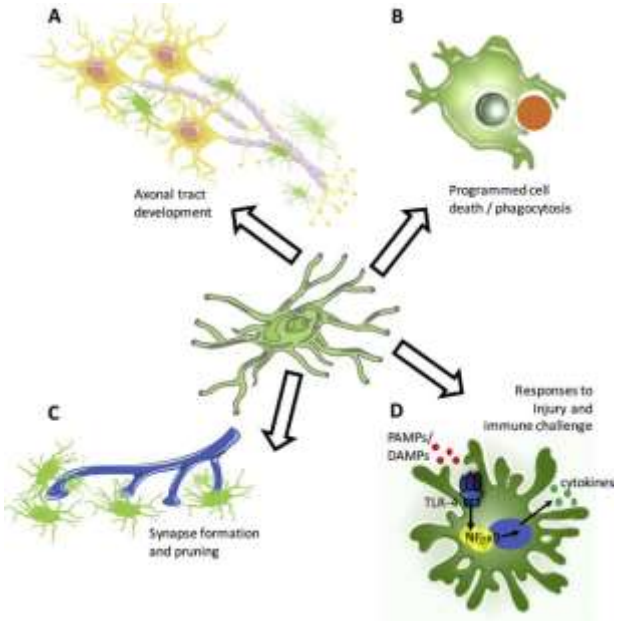
Potential mechanisms triggering radiation-induced cognitive impairment are:

- vascular damage (BBB Disruption),
- decline in oligodendrocytes and other glial cells,
- neuroinflammation caused by activated microglia,
- impaired hippocampal neurogenesis,
- altered function of adult neurons.

Neuroinflammation caused by activated microglia

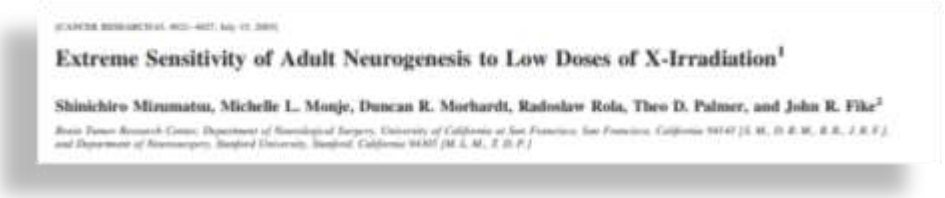
Microglia are resident mononuclear phagocytes that maintain brain microenvironment homeostasis and provide immune defense. After insults to the brain they become activated by rounding of the cell body, retraction of cell processes and proliferation. Microglia activation plays an important role in phagocytosis of dead cells.





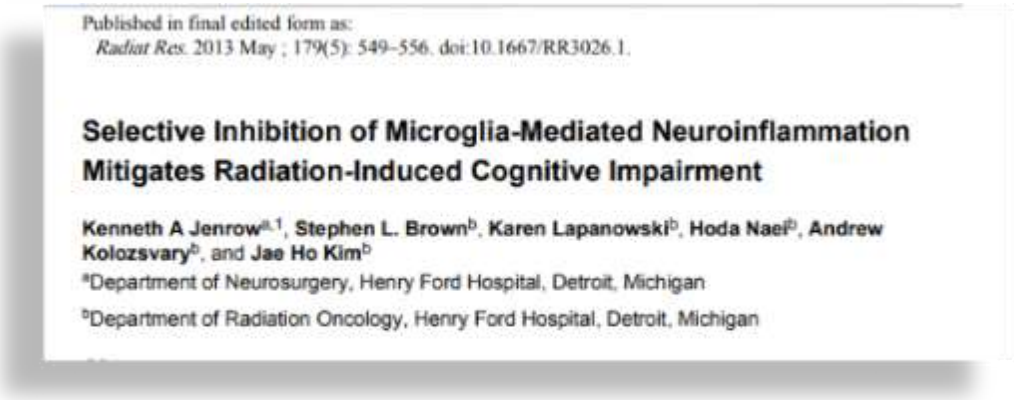
However, persistent microglia activation contributes to chronic inflammation, (i) **negatively affects neuronal structures**, (ii) **results in decreased synaptic plasticity** and **has been implicated in the pathophysiology of brain injury**. Activated microglial cells initiate an inflammatory response by releasing pro-inflammatory cytokines and ROS. This pro-inflammatory state can be cytotoxic to surrounding cells and can propagate tissue damage and cause secondary injury.

Neuroinflammation caused by activated microglia



Extreme Sensitivity of Adult Neurogenesis to Low Doses of X-Irradiation[1]

Shinichiro Mizumatsu, Michelle L. Monje, Duncan R. Morhardt, Radoslaw Rola, Theo D. Palmer, and John R. Fike[2]



Published in final edited form as:
Radiat Res. 2013 May ; 179(5): 549–556. doi:10.1667/RR3026.1.

Selective Inhibition of Microglia-Mediated Neuroinflammation Mitigates Radiation-Induced Cognitive Impairment

Kenneth A Jenrow[a,1], **Stephen L. Brown**[b], **Karen Lapanowski**[b], **Hoda Naei**[b], **Andrew Kolozsvary**[b], and **Jae Ho Kim**[b]

[a]Department of Neurosurgery, Henry Ford Hospital, Detroit, Michigan

[b]Department of Radiation Oncology, Henry Ford Hospital, Detroit, Michigan

Microglia activation might be detected even months after irradiation indicating the persistence of neuroinflammatory process

Therapy with MW-151, a selective inhibitor of proinflammatory microglial cytokines, was initiated 24 h after 10 Gy whole-brain irradiation (WBI) administered as a single fraction and **maintained for 28 days thereafter**.

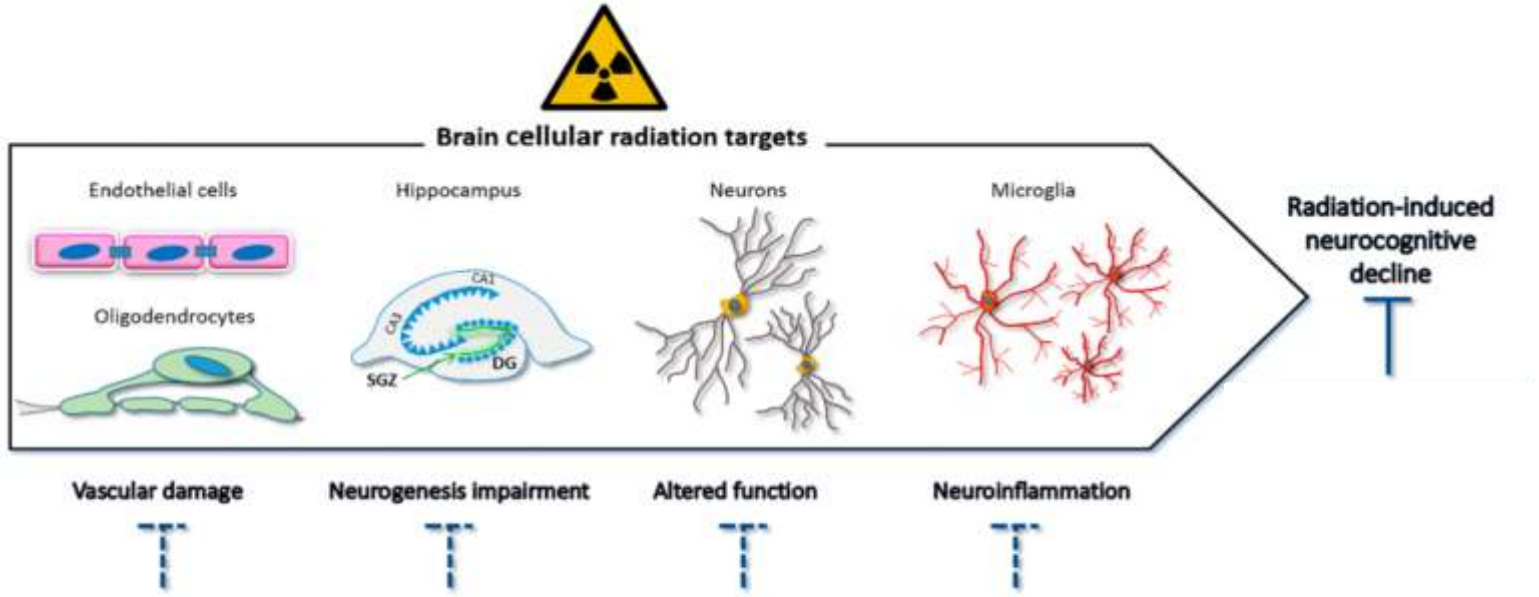
(i) mitigated radiation-induced neuroinflammation at 2 and 9 months post-WBI

(ii) potently mitigated radiation induced deficits of “novel object recognition consolidation” and of “long-term potentiation induction and maintenance”.

These results suggested that transient administration of MW-151 was sufficient to prevent irradiation-induced cognitive impairment

Mechanisms of radiation-induced brain injury

Brain radiation injury is multifactorial and complex, involving dynamic interactions between multiple cell types



Potential mechanisms triggering radiation-induced cognitive impairment are:

- vascular damage (BBB Disruption),
- decline in oligodendrocytes and other glial cells,
- neuroinflammation caused by activated microglia,
- impaired hippocampal neurogenesis,
- altered function of adult neurons.

Timelines of neurogenesis discovery

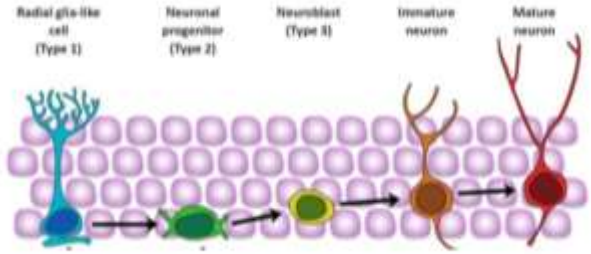
In the **1960**s, it was first discovered that, similar to other vertebrates, such as fish and amphibians, adult **neurogenesis** also occurs in **mammals**: new nervous system cells continue to grow in the brain, even as animals get older.

Postnatal Neurogenesis in the Guinea-pig

by
JOSEPH ALTMAN
GOPAL D. DAS

Psychophysiological Laboratory,
Massachusetts Institute of Technology,
Cambridge, Massachusetts

The young of rats and mice are immature at birth. After birth, their brains grow in size and there is also a marked proliferation of cells which become differentiated into neurones with short axons (micro-neurones). The proliferation of similar cells has now been demonstrated in the hippocampus of postnatal guinea-pigs even though these rodents are born with nearly full-size brains.



More hippocampal neurons in adult mice living in an enriched environment

Gerd Kempermann, H. Georg Kuhn & Fred H. Gage

The Salk Institute for Biological Studies, Laboratory of Genetics, 10010 North Torrey Pines Road, La Jolla, California 92037, USA

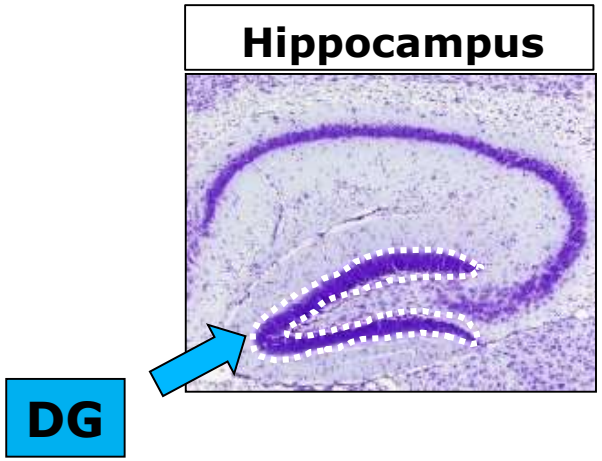
NATURE | VOL 386 | 3 APRIL 1997

In **1998** was demonstrated that neurogenesis takes place in the adult human brain throughout the life cycle

Neurogenesis in the adult human hippocampus

PETER S. ERIKSSON[1,2], EKATERINA PERFILIEVA[1], THOMAS BJÖRK-ERIKSSON[2], ANN-MARIE ALBORN[1], CLAES NORDBORG[3], DANIEL A. PETERSON[4] & FRED H. GAGE[4]

Neurogenesis in the hippocampus



- The hippocampus is one of the major sites of adult neurogenesis in both humans and rodents.
- Learning memory is dependent on proper hippocampus functionality.
- Abnormalities in the hippocampal neurogenesis are also related with neurological disorders such as epilepsy, Alzheimer's disease and depression.

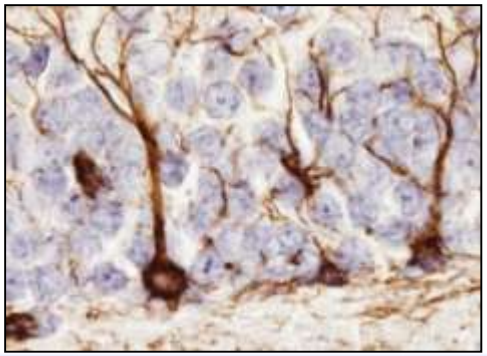
In the dentate gyrus (DG) of the hippocampus continuous neurogenesis is observed throughout life and the majority of neurons are generated postnatally.

Thousands of new neurons are produced in the DG of rodents each day

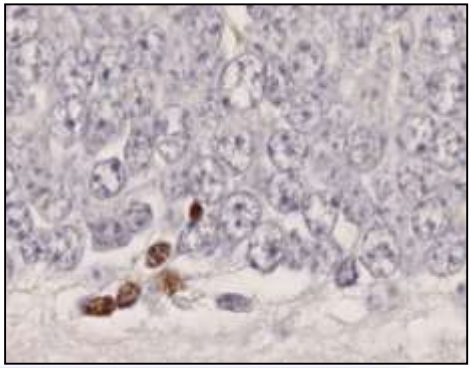
Hippocampus adult neurogenesis is a multistep process

Different cellular populations reside in the DG, distinguishable for their morphology and expression of cellular markers

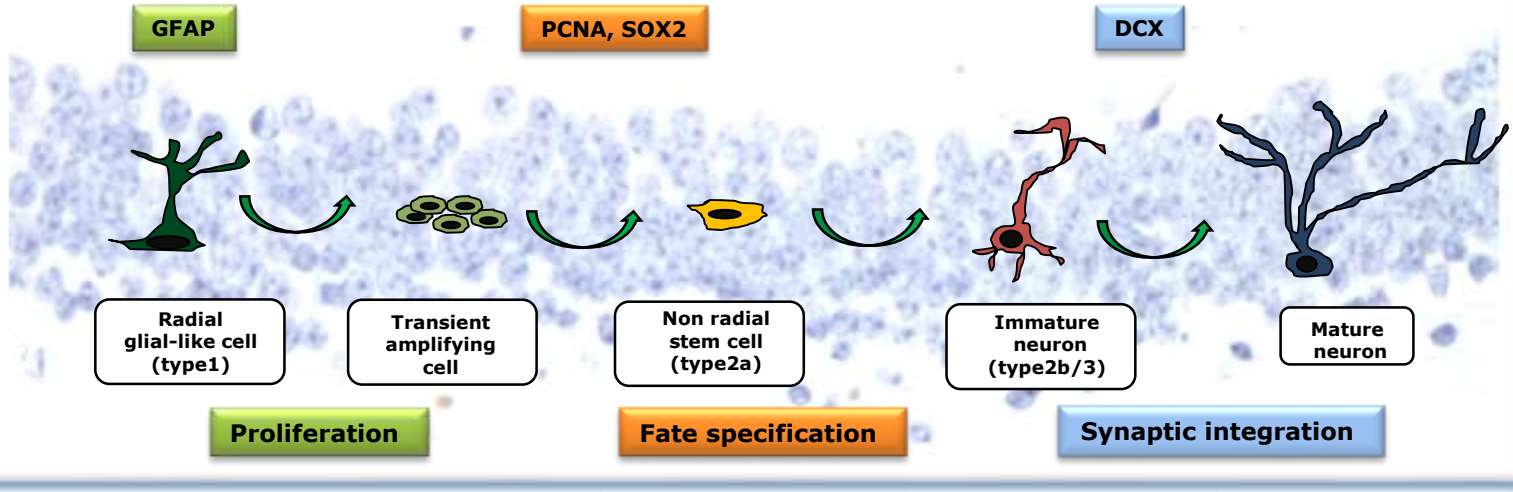
GFAP



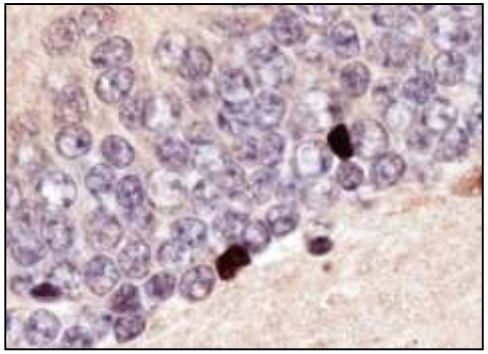
PCNA



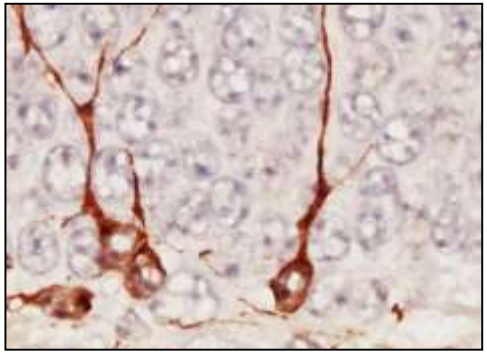
Dentate gyrus



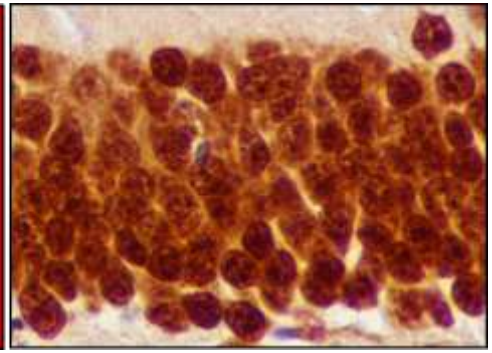
SOX2



DCX



NeuN



Radiation-induced impairment of hippocampal neurogenesis

Impairment of **neurogenesis** in the hippocampus following whole-brain irradiation is referred as one of the most important mechanisms of radiation-induced cognitive dysfunction

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Experimental Neurology

Radiation-induced impairment of hippocampal neurogenesis is associated with cognitive deficits in young mice

Radoslaw Rola,[a] Jacob Raber,[b,c,d] Angela Rizk,[b] Shinji Otsuka,[a] Scott R. VandenBerg,[a,c] Duncan R. Morhardt,[a] and John R. Fike[a,*]

5 Gy

21 days-old C57Bl6 mice

1-3 months postirradiation

Decrease in DG neurogenesis

Table 1
The fate of newly born cells produced by surviving precursor cells assessed by BrdU labeling with subsequent use of cell-specific antibodies

Cell line marker	Percentage of double-labeled cells (mean ± SEM)					
	1 month after irradiation			3 months after irradiation		
	Control	Irradiated	P	Control	Irradiated	P
NeuN	78.52 ± 4.69	43.41 ± 2.46	0.02	60.39 ± 1.55	37.38 ± 1.77	0.03
GFAP	8.97 ± 0.60	12.01 ± 1.70	ns	5.04 ± 0.75	10.34 ± 0.48	0.03
NG2	3.52 ± 0.46	8.76 ± 1.23	0.03	7.04 ± 3.65	9.22 ± 3.33	ns
CD68	17.45 ± 1.16	43.82 ± 3.59	0.03	14.15 ± 1.44	35.56 ± 3.88	0.03
CD68/NG2	0.6 ± 0.32	6.2 ± 1.65	0.03	1.34 ± 0.49	4.39 ± 1.48	ns

Overall BrdU-positive cells number was reduced by ~70% after 5 Gy.
NeuN—neuron-specific nuclear protein, GFAP—glial fibrillary acidic protein, NG2—chondroitin sulfate proteoglycan, CD68—macrosialin, CD68/NG2.

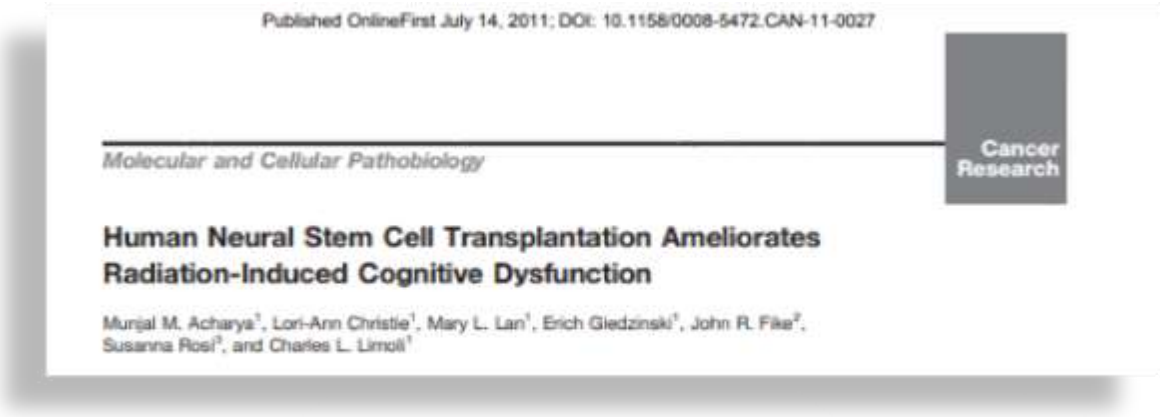
Chronic inflammatory response:
- **Activated microglia**
- **Infiltrating peripheral monocytes**

Deficit in spatial memory retention using Morris water maze

Irradiation of young animals induce long-term impairment of neurogenesis associated with deficit in hippocampal-dependent task

Stem cell replacement as a strategy to combat radiation-induced cognitive decline

Cognitive function can be partially rescued by neural stem cell transplantation to replace the lost hippocampal NPCs following the whole-brain irradiation in rodents


Published OnlineFirst July 14, 2011; DOI: 10.1158/0008-5472.CAN-11-0027

Molecular and Cellular Pathobiology

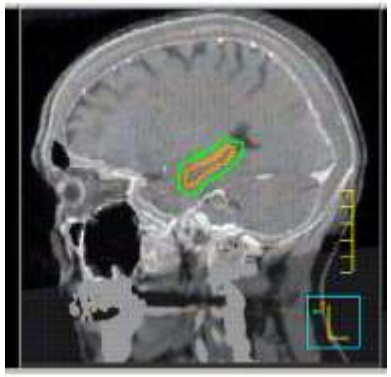
Cancer Research

Human Neural Stem Cell Transplantation Ameliorates Radiation-Induced Cognitive Dysfunction

Munjal M. Acharya[1], Lori-Ann Christie[1], Mary L. Lan[1], Erich Giedzinski[1], John R. Fike[2], Susanna Rosi[3], and Charles L. Limoli[1]

The potential of using stem cell replacement as a strategy to combat radiation-induced cognitive decline was addressed by **irradiating athymic nude rats** followed 2 days later by **intrahippocampal transplantation** with human neural stem cells (**hNSC**). Measures of cognitive performance, at **1 and 4 months after irradiation** showed that **irradiated animals engrafted with hNSCs exhibited significantly less decline in cognitive function than irradiated**, sham-engrafted animals and **acted indistinguishably from unirradiated controls**. **These data show that hNSCs afford a promising strategy for functionally restoring cognition in irradiated animals**.

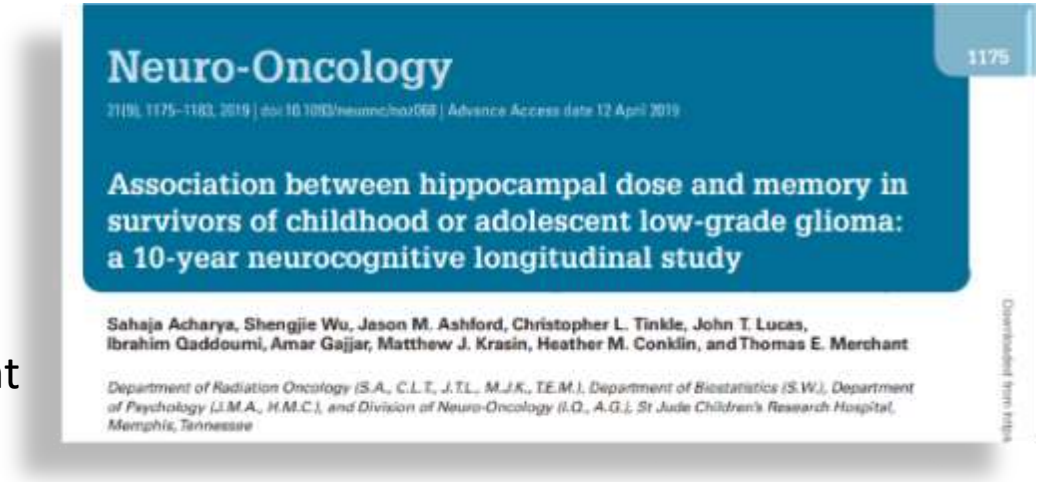
Hippocampus avoidance (HA)



The importance of hippocampus in the pathogenesis of radiation-induced neurocognitive effects is also underlined by the observation that hippocampal avoidance reduce short-term memory decline in adults receiving whole-brain radiation therapy (Gondi et a., 2014)

Key Points

- Survivors of pediatric low-grade gliomas experience decline in memory.
- Greater hippocampal dose is associated with greater decline in memory.
- Reducing hippocampal dose may represent a memory preserving treatment strategy.



Neuro-Oncology

1175

Association between hippocampal dose and memory in survivors of childhood or adolescent low-grade glioma: a 10-year neurocognitive longitudinal study

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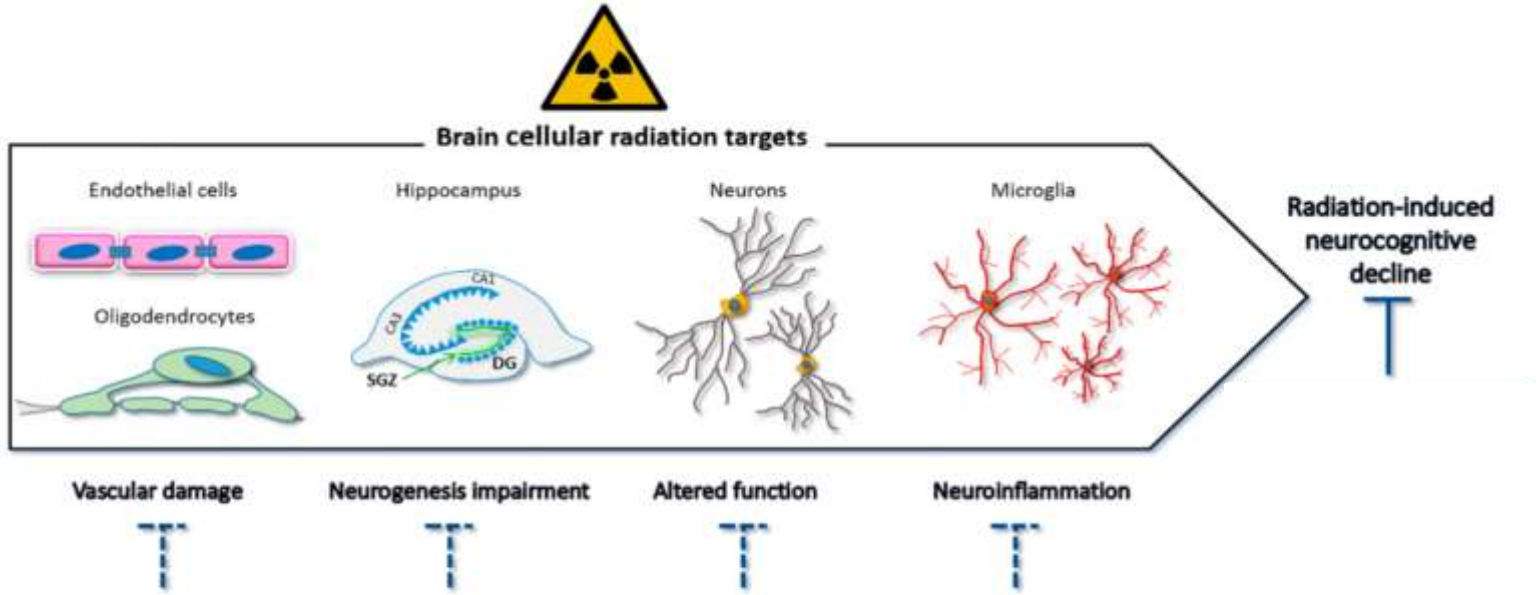
Although the merit of HA in pediatric brain tumor patients is still unexplored, it may be greater in children than adults, because of the higher vulnerability to radiation injury.

Mechanisms of radiation-induced brain injury

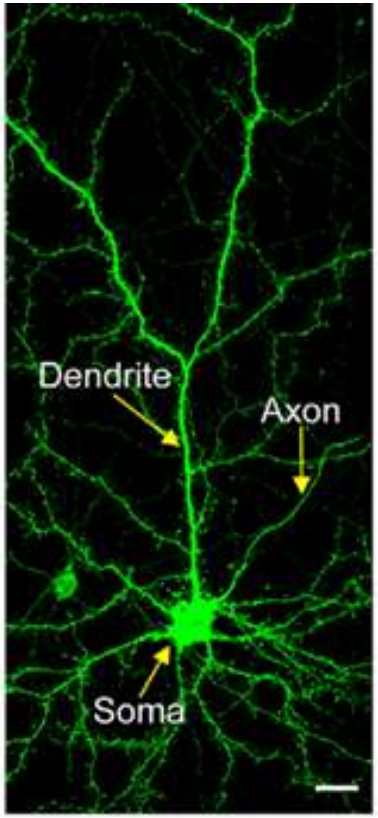
Brain radiation injury is multifactorial and complex, involving dynamic interactions between multiple cell types



Potential mechanisms triggering radiation-induced cognitive impairment are:

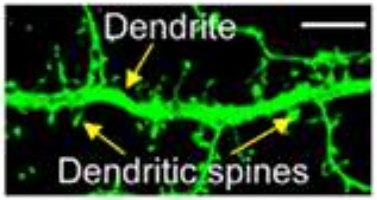
- vascular damage (BBB Disruption),
- decline in oligodendrocytes and other glial cells,
- neuroinflammation caused by activated microglia,
- impaired hippocampal neurogenesis,
- altered function of adult neurons.

Altered function in neurons



Dendrites, the branched projections of a neuron, are essential for synaptic contacts. Thus dendritic morphology is important for many aspects of neural function, including signal propagation and information processing.

Spines undergo experience-dependent morphological changes in live animals and even small changes in dendritic spines may have marked effects on synaptic function, plasticity and patterns of connectivity in neuronal circuits.



Notably, disease-specific disruptions in **dendritic spine shape**, **size** or **number** accompany a large number of brain disorders.

Dendritic spine pathology in neuropsychiatric disorders

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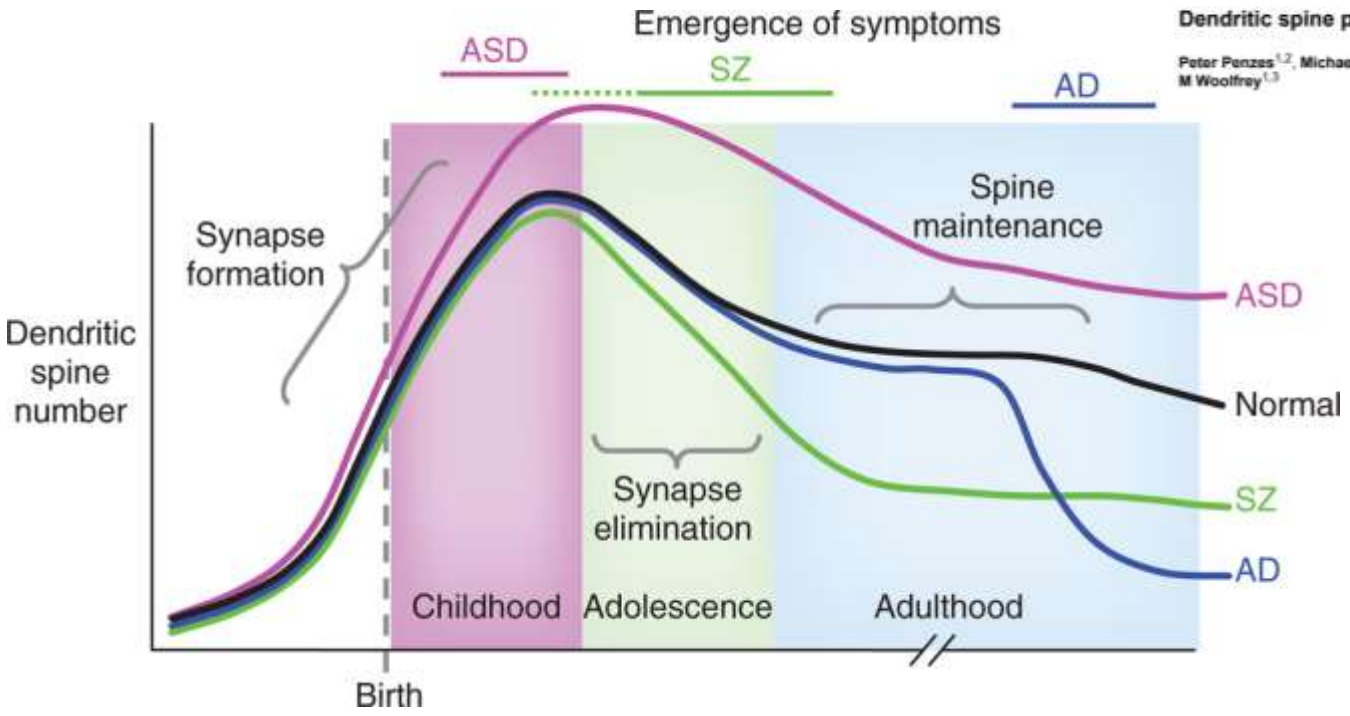
Dendritic spine pathology in neuropsychiatric disorders

Peter Penzes[1,2], Michael E Cahill[1,2], Kelly A Jones[1,2], Jon-Eric VanLeeuwen[1,2], and Kevin M Woolfrey[1,2]



In normal subjects, spine numbers increase before and after birth; spines are selectively eliminated during childhood and adolescence to adult levels. In **ASD**, exaggerated spine formation or incomplete pruning in childhood may lead to **increased spine numbers**. I**n schizophrenia**, **exaggerated spine pruning in late childhood** or **adolescence** may lead to the emergence of symptoms. In **Alzheimer's disease**, **spines are** rapidly **lost in late adulthood**, suggesting perturbed spine maintenance mechanisms that may underlie cognitive decline.

Altered function of mature neurons after irradiation

Brain has been clasically regarded as a radioresistant organ, and neurons as essentially inert to radiation

PNAS

Cranial irradiation compromises neuronal architecture in the hippocampus

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Brain Struct Funct (2015) 220:1161–1171
DOI 10.1007/s00429-014-0709-9

ORIGINAL ARTICLE

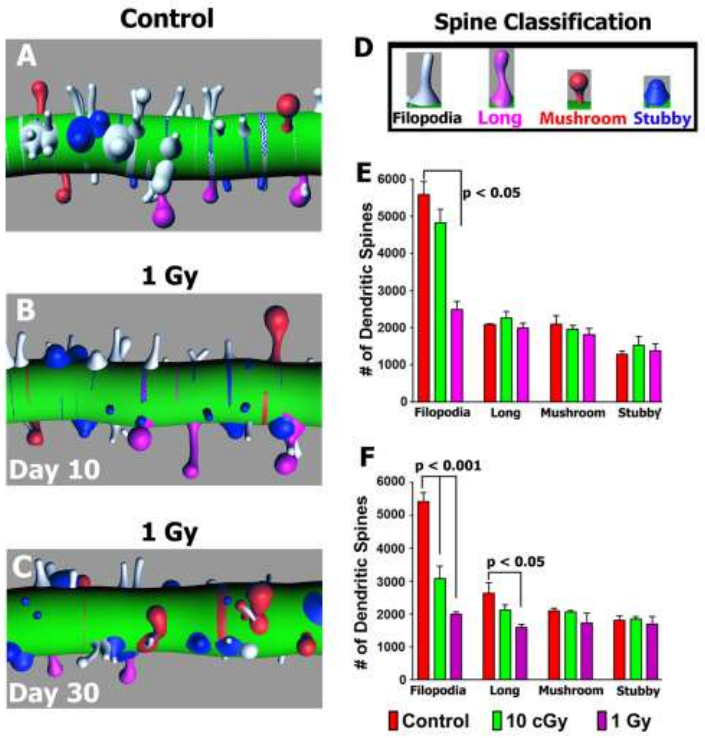
Persistent changes in neuronal structure and synaptic plasticity caused by proton irradiation

Vipan K. Parihar · Junaid Pasha · Katherine K. Tran · Brianna M. Craver · Munjal M. Acharya · Charles L. Limoli

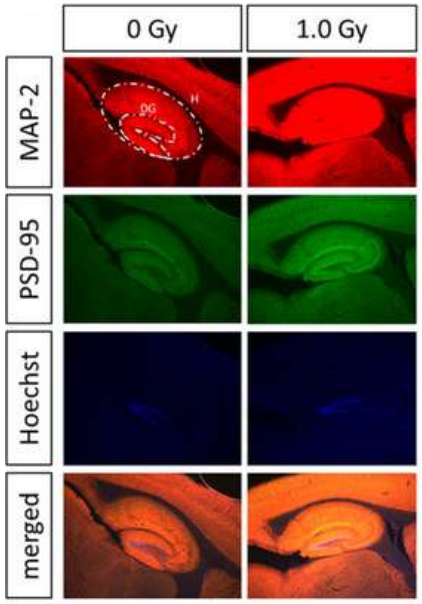
Two studies documented dose-dependent (0,1-1 Gy) and persistent (**10 and 30 days postirradiation**) reduction in dendritic complexity in mouse hippocampal neurons, detected as a **reduction in dendrite branching lenght** compared to unexposed control. **Immature fillpodia, showed the gratest radiation sensitivity** compared to mature spine morphologies such as mushrooms type.

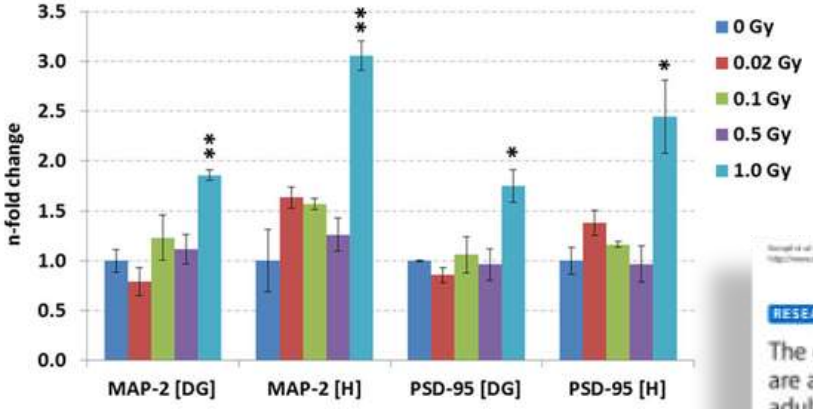
Radiation-induced adverse effects on cognition may also be promoted by alterations in mature neuronal networks

Brain Struct Funct (2015) 220:1161–1171



Alteration in synaptic proteins in the hippocampus after irradiation





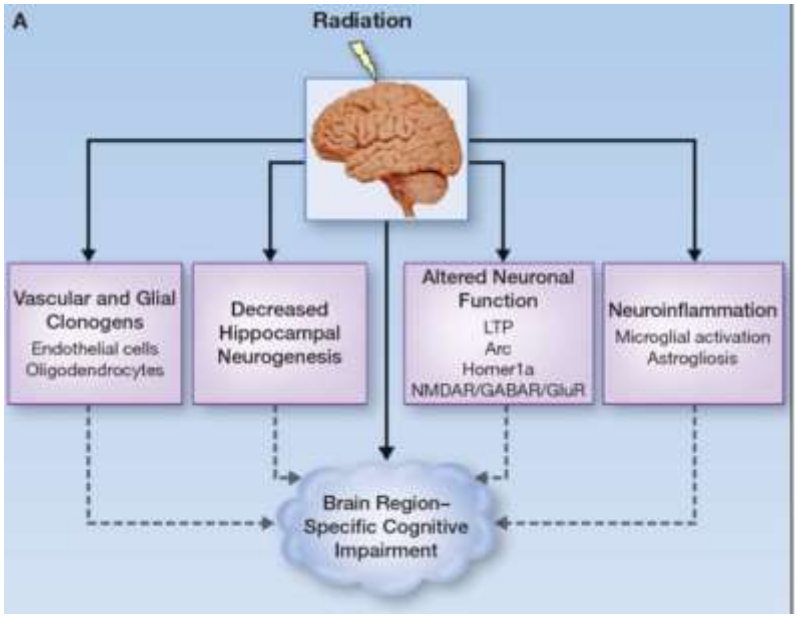

RESEARCH ARTICLE Open Access

The cognitive defects of neonatally irradiated mice are accompanied by changed synaptic plasticity, adult neurogenesis and neuroinflammation

Long-term increased expression of postsynaptic density protein (**PSD-95**) and microtubule-associated protein 2 (**MAP-2**) have been reported in the hippocampus after radiation exposure of mice. These proteins have a role in spine formation and and maturation and stability of dendrites (Kempf et al., 2014).

Dendritic spine pathology and altered expression of synaptic proteins may therefore be one of the pathophysiological mechanisms in radiation-induced brain damage.

Summary for the mechanisms of radiation-induced brain injury



Irradiation induces a wide spectrum of cellular damage that elicits a global stress response. The complexity of neurocognitive effects after irradiation cannot be fully explained by alteration of a single cell type, and the pathogenesis of **radiation-induced cognitive injury is likely dependent on dynamic connections between multiple cell types (i.e., neurons, microglia and astrocytes)**.

Radiation doses

- Much focus has been directed towards adverse radiation effects following **radiotherapeutic doses**, less is known on how exposure to **low/moderate doses** affects normal brain development **during early postnatal life**

- Molecular mechanisms at high doses might be different from those acting at low dose

Increasing uses of X-rays in diagnosis

C**omputed tomography (CT)** has been established as one of the most informative diagnostic radiology examinations. **The use of CT scans has increased over the past decades and particularly in the field of pediatric diagnostic and adult screening**.

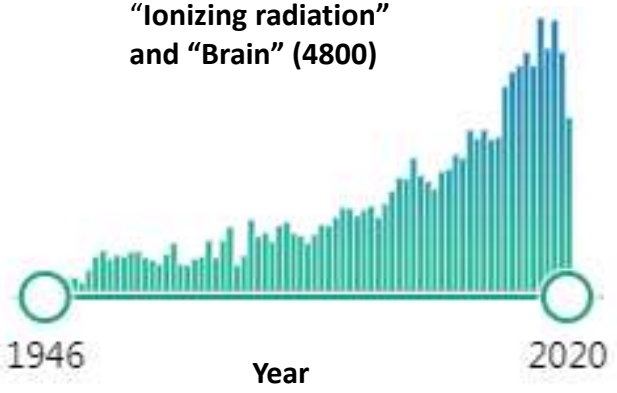
CT scans are accountable for 40-70% of the medical dose in the population (Brenner et al., 2012) and **head CT scans contributed to almost 15% of the total collective effective dose in the general population** (Mettler et al., 2000; Mettler et al., 2008).

The growing use of CT procedures on children raises concern over the long-term health risk, because of the radiosensitivity of children. Estimations of brain doses during CT scans show an increasing trend with decreasing patient age. Children under 5 years of age are exposed to an absorbed dose in the range of **50/100 mGy/scan** (Brenner and Hall, 2007; Trattner et al., 2014).

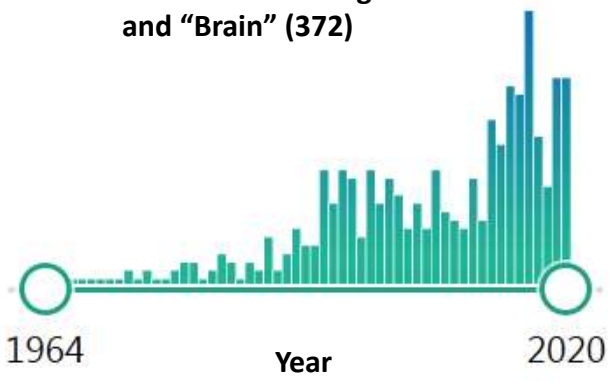
Publications trends in PubMed

A large amount of uncertainty remains concerning the impact of low dose ionizing radiation on the brain

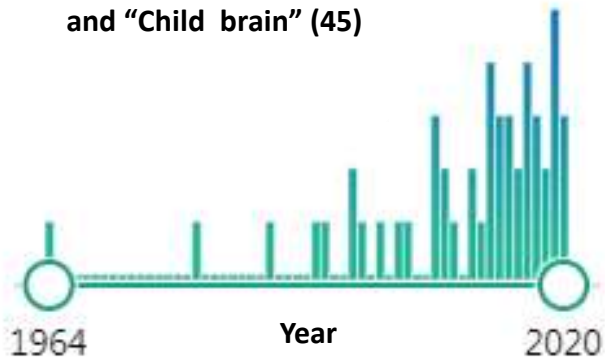
"Ionizing radiation" and "Brain" (4800)



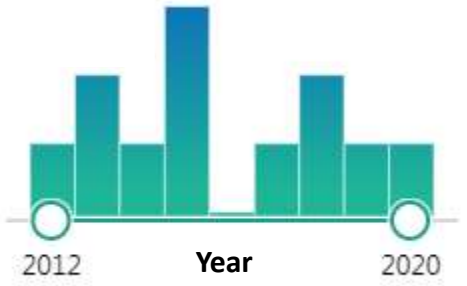
"Low dose ionizing radiation" and "Brain" (372)



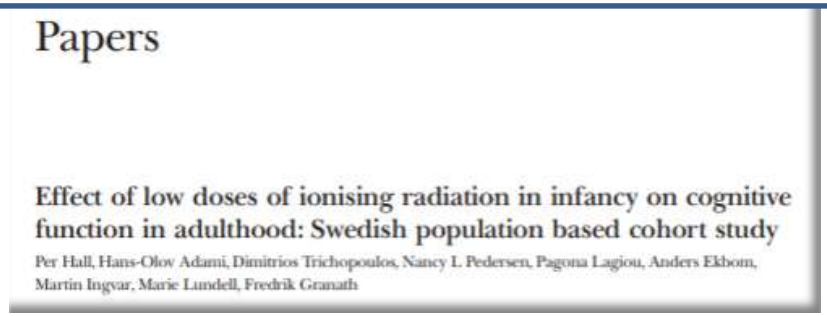
"Low dose ionizing radiation" and "Child brain" (45)



"Low dose ionizing radiation" and "Neurocognitive effects" (10)



LOW DOSE radiations effects on the brain


Papers

Effect of low doses of ionising radiation in infancy on cognitive function in adulthood: Swedish population based cohort study

Per Hall, Hans-Olov Adami, Dimitrios Trichopoulos, Nancy L Pedersen, Pagona Lagiou, Anders Ekbom, Martin Ingvar, Marie Lundell, Fredrik Granath

The publication of results of the Swedish Haemangioma study (Hall et al. 2004) associating low radiation doses (120-150 mGy) during infancy with cognitive decline during adult life, stimulates interest in the potential non-cancer effects of low/moderate doses of ionizing radiation.


Environment International

Volume 136, March 2020, 105371

ELSEVIER

Neurodevelopmental effects of low dose ionizing radiation exposure: A systematic review of the epidemiological evidence

Elisa Pasqual, Magda Bosch de Basea, Mónica López-Vicente, Isabelle Thierry-Chef, Elisabeth Cardis

This recent review examined neurodevelopmental effects of low/moderate doses received during fetal life, childhood and adolescence. A total of 26 manuscripts were finally selected.

Most informative studies: - A-bomb survivors
- Tinea capitis
- Haemangioma cohorts

Highlights

- Selected studies were heterogeneous in terms of outcome and exposure assessment.
- The strength of evidence for an effect on general cognition and language was *limited*.
- The evidence for an effect on other neurodevelopment domains was *inadequate*.

To implement epidemiological studies on cognitive radiation-induced effects, small size of the cohorts, limited dose estimation, confounding factors and low outcome specificity for cognitive measure have to be overcome

Recent EURATOM Funded Project involving research on neurocognitive radiation effects

CEREBRAD (2011-2015) - **Cognitive and Cerebrovascular Effects Induced by Low Dose Ionising Radiation**

Goal: to assess long-term cellular and molecular alterations induced by low-dose irradiation

CEREBRAD

1/10/2011-31/03/2015

Cognitive and Cerebrovascular Effects Induced by Low Dose Ionising Radiation

Experimental scheme

Irradiation at low/moderate doses	Behaviour, learning and memory tests	IHC and molecular analysis of the hippocampus

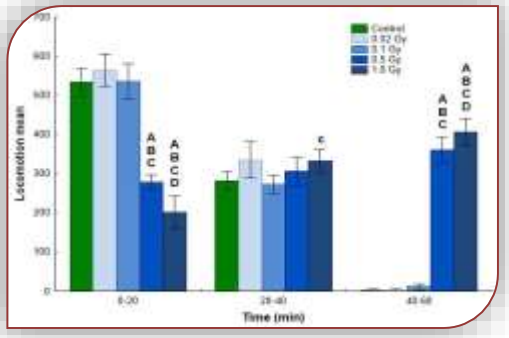
P10 → 2-6 months → 1-6 months

Mice at P10 were whole-body irradiated, subjected to behavioral tests between 2 and 6 months of age and evaluated for changes in adult hippocampal neurogenesis.

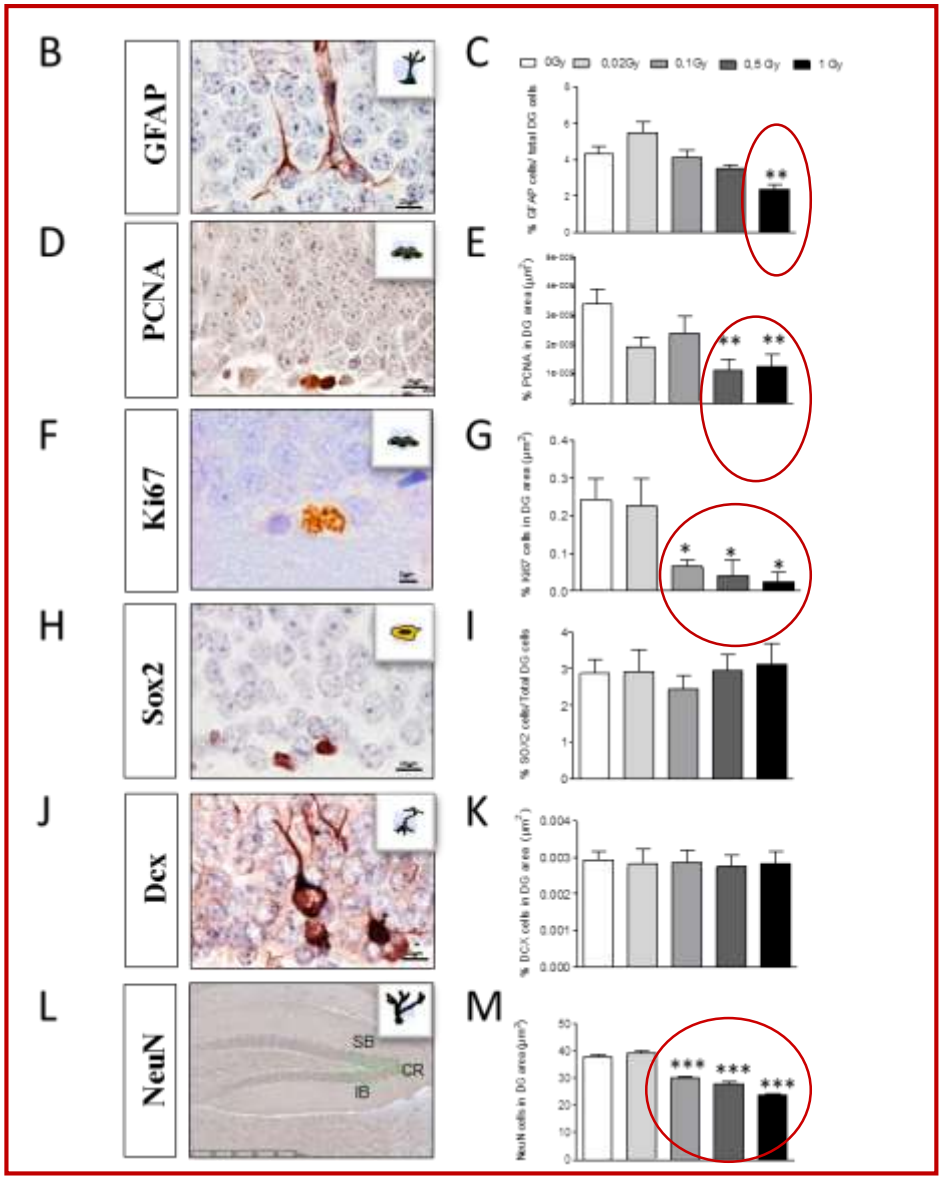
Histopathological hallmarks induced by γ-rays in the hippocampus of NMRI mice exposed PN10

PN10 NMRI

We were able to demonstrate significant depletion of RGL (GFAP⁺), proliferative precursors (PCNA⁺ and Ki67⁺), and mature neurons (NeuN+) at 6 months postirradiation



Persistent impairment of memory and cognition was detected at doses ≥ 500 mGy.

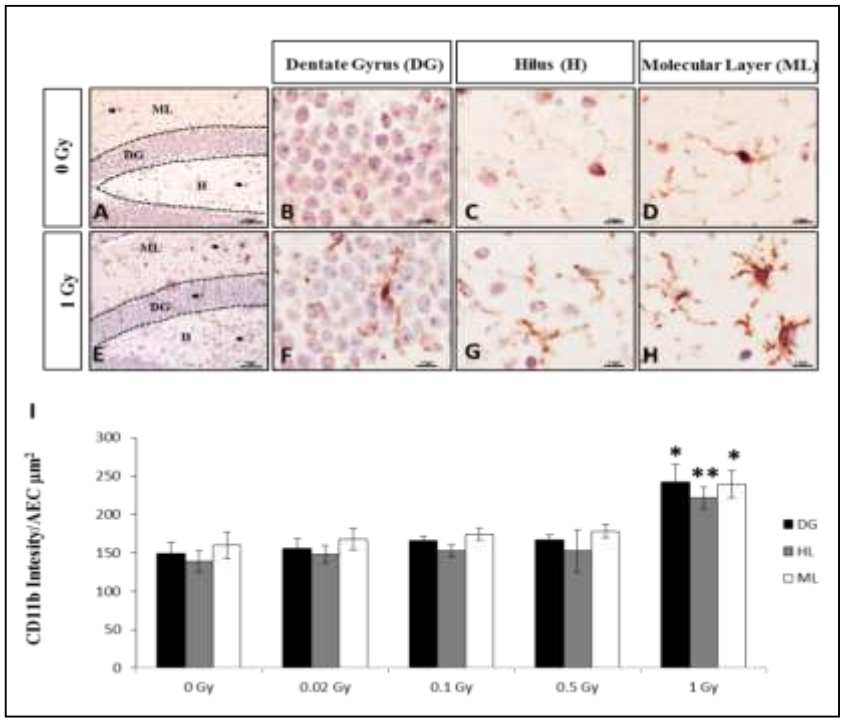


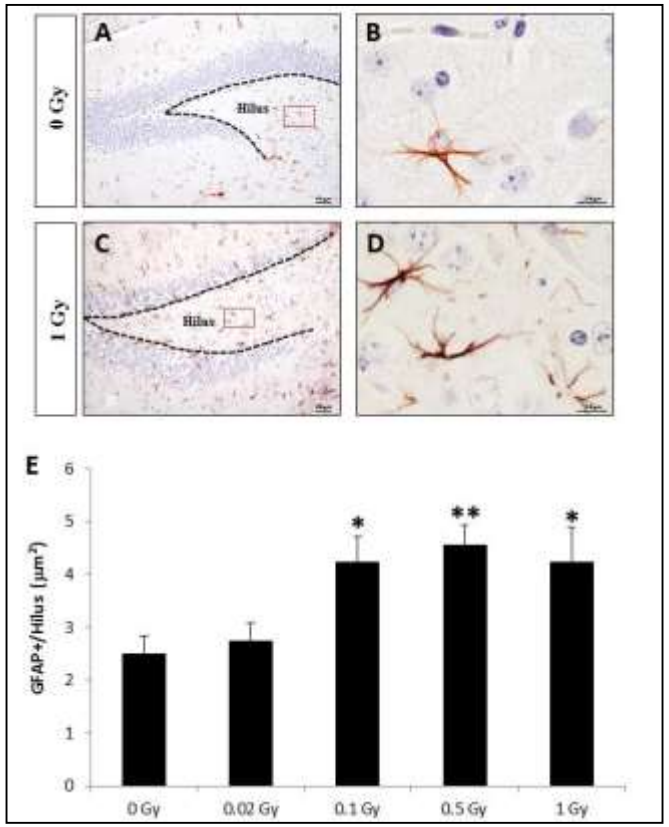
Histopathological hallmarks induced by γ-rays in the hippocampus of NMRI mice exposed at PN10

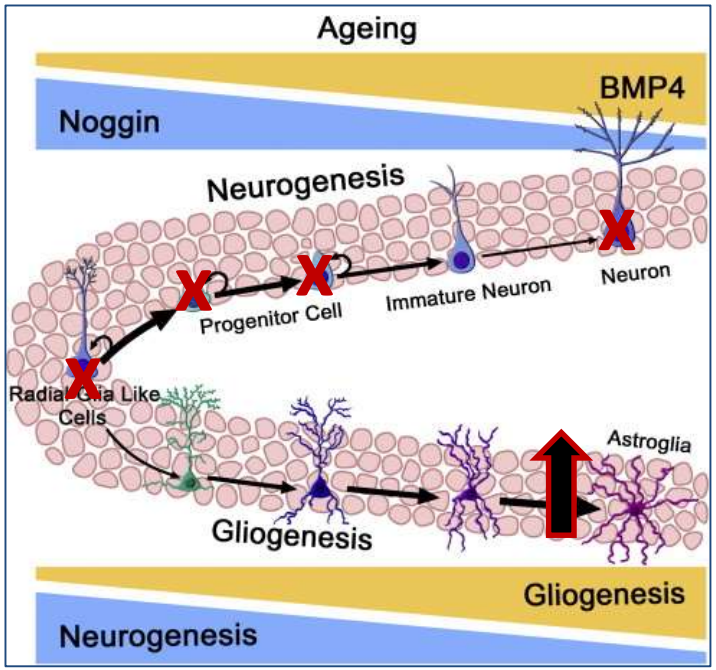
Microenvironment is another critical player in hippocampal neurogenesis

PN10 NMRI

- **Microglia** activation (CD11b) and increased number of GFAP⁺ **astrocytes** in the hilus after irradiation indicate a persistent **neuroinflammation** after exposure to low/moderate radiation doses (0.1-1Gy).

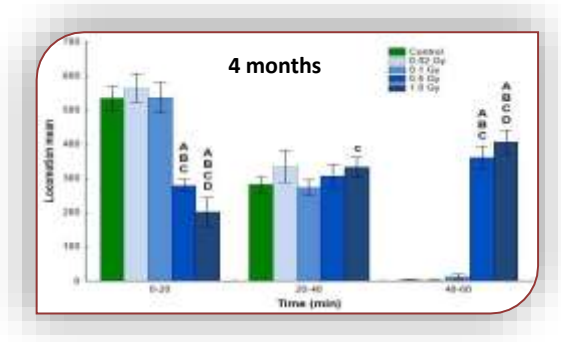






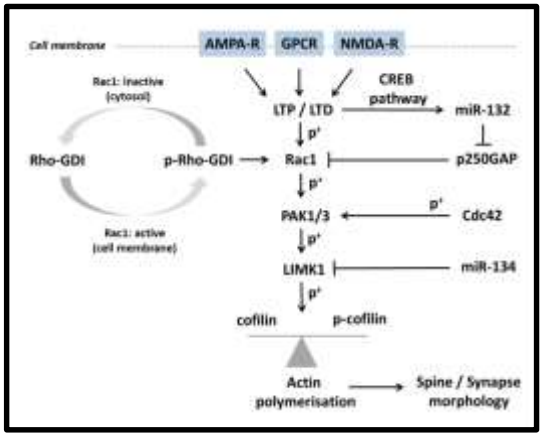
Ionising Radiation impairs adult neurogenesis and induces chronic inflammation processes

ENEA



Irradiation Alters Cognitive Function

Uppsala University



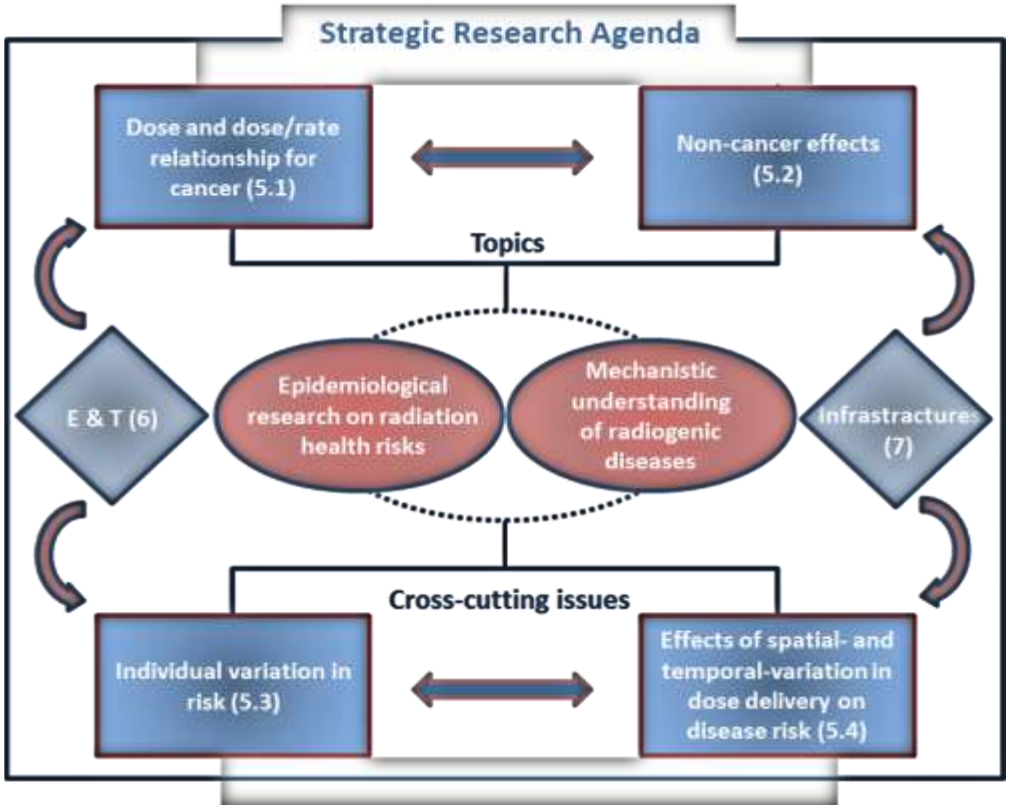
Ionising Radiation Affects Synaptogenesis

Helmholtz Zentrum

Both neurological and behavioral effects were detectd at dose ≧ 0.5 Gy
suggesting a threshold around this dose for hippocampal-dependent memory deficit

MELODI SRA

Assessing the effect of low/moderate doses of ionizing radiations on non-cancer effects, including neurocognitive decline, is a key priority set-out in the current MELODI SRA, in terms of both epidemiological and mechanistic studies



Interdidisciplinary group of experts with expertise in neurocognitive radiation effects

Epidemiologists Biologists

Dosimetrists Clinitians

Environment International

Cognitive effects of low dose of Ionizing Radiation exposure – lessons learnt and research gaps

--Manuscript Draft--

Manuscript Number:	
Article Type:	VSI: Radiation non-cancer
Keywords:	cognition, ionizing radiation, low doses, atomic bombing, Chernobyl accident, medical radiation
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	Mohammed Abderrafi Benotmane
	Elisabeth Cardis

(i) Summarise the state of knowledge

(ii) Research recommendations for future studies

(i) Overall evidences were presented of cognitive effects for low/moderate doses radiation both from biology and epidemiology

(ii) For future studies, efforts are needed for (**a**) a better characterization of the effects, including specific cognitive functions or disease affected by radiation exposure and (**b**) better understanding of the mechanisms

Experimental gaps and recommendations for future studies

Cognitive decline at low/moderate radiation doses is challanging to address in **epidemiological studies**

- Considering the effect modification of **age at exposure** and **age at cognitive assessment** is an important issue for the interpretation of results of epidemiological studies

- Understanding of the **effect of co-exposure** in particular medical settings is also important.

- Notwithstanding the importance of rodent models in elucidating the pathogenesis of radiation-induced cognitive effects, the validity for humans should also be investigated. To this aim establishing brain-tissue bank/s from large patient cohorts, open to researchers is needed.

- Research on the mechanisms acting at low/moderate radiation dose, that may not be identical to those at high dose, has to be fostered

Multidisciplinary approaches including collection of suitable biological samples, comprehensive cognitive function assessment, precise dosimetry to different brain structures and multi-omic approches to elucidate genetic and epigenetic mechanisms of radiation-induced neurocognitive effects at low/moderate radiation doses should be implemented

Other recommendations….

- Identification of genetic susceptibility factors in radiation-induced cognitive dysfunction at low doses in children

- Further mechanistic investigations on the contribution of «out-of-target» neurocognitive effects

- Investigation on long-term neurocognitive benefits of proton therapy for pediatric patients with brain tumor and related mechanistic experimental studies in mice

- Long-term neurocognitive benefits of Ultra-high dose-rate (>100 Gys^{-1}) FLASH radiotherapy to spare healthy tissues

Overall, more research in large epidemiological cohorts and animal models are needed to improve the understanding of radiation-induced cognitive effects. Results may then be translated into recommendations for improving radiation protection of patients undergoing diagnostic and therapeutic medical procedures

Conclusions

Recognition of children's vulnerability to radiation effects, should in turn, stimulate substantial investments in children's health research. **To protect human health, and especially the health of infants and children, should be the paradigm for radiation protection.**


THANK YOU