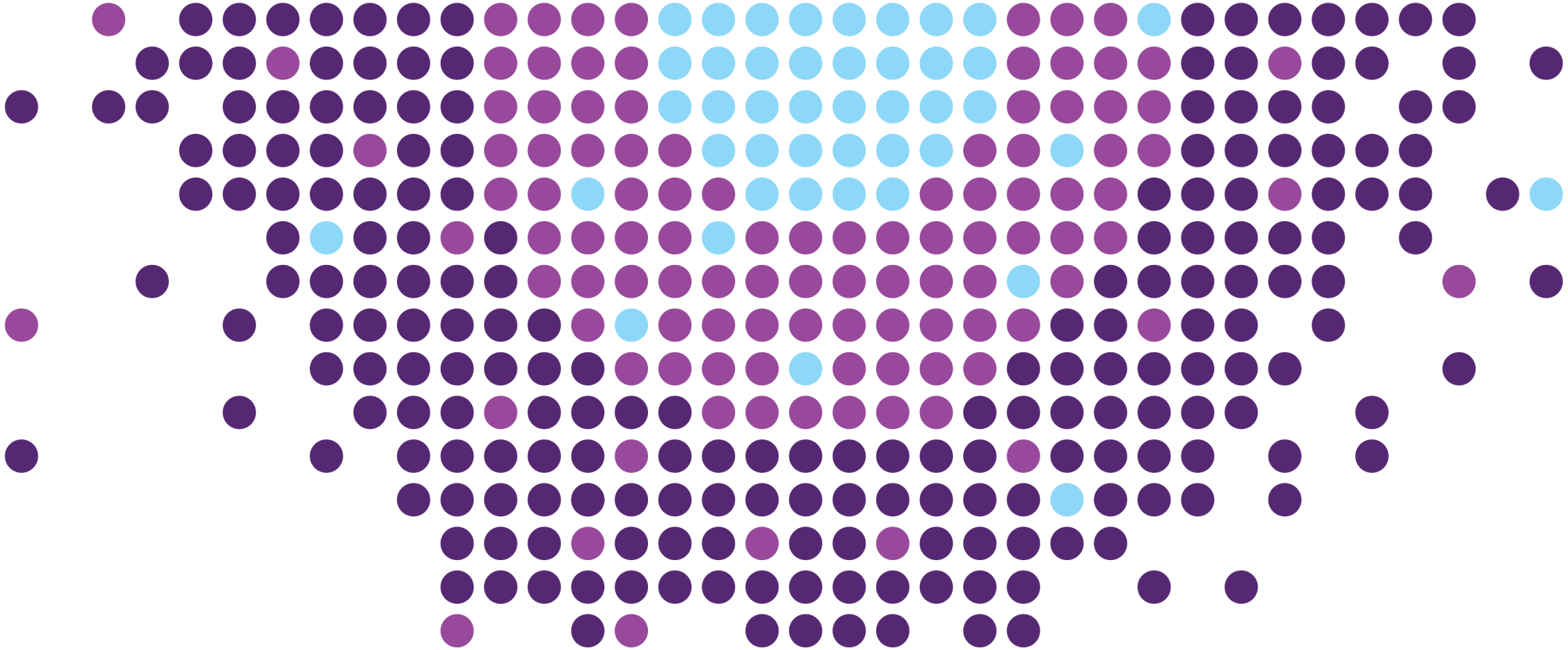


sck cen
Belgian Nuclear Research Centre

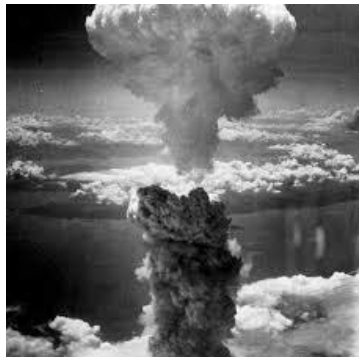
Mieke Verslegers - 16/10/2020 - BVS-ABR Young Scientist Event

Neurocognitive dysfunction and signs of brain aging in response to early-life irradiation

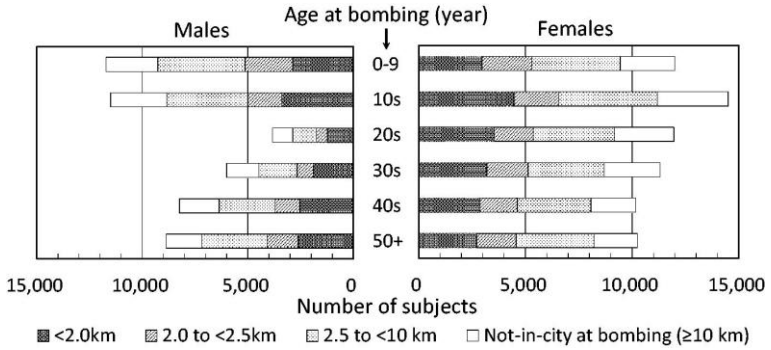
- Epidemiological evidence
- Experimental data
- A link with neurodegenerative disorders?

Epidemiological evidence

Historical exposures



Number of LSS subjects by sex, age at bombings, and distance from hypocenters



Ozasa, 2019, Int J Rad Biol

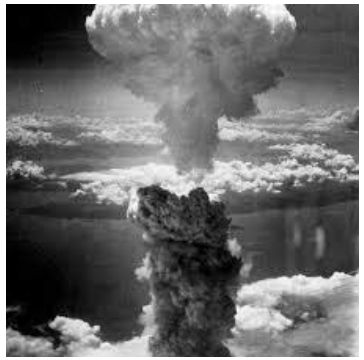
TABLE 1. Child population, by residency at time of accident, Israeli Chernobyl Health Effects Study, 1998–2001

Residential area	Level of cesium 137 (Ci/km²)*	No. of children approached	Participating children		Children in utero at time of accident	
			No.	%	No.	%
Gomel region, Belarus, and other exposed areas in Belarus and the Ukraine	1–40	1,169	667†	57.0	98	15
Mogilev region, Belarus	<1	216	130	60.2	14	11
Kiev region, the Ukraine	<1	506	278	54.9	48	17
Other regions in Belarus	≤0.1	598	372	62.0	72	19
Cities of Moscow and St. Petersburg, Russia	≤0.1	280	182	65.0	38	21
Total		2,769	1,629		270	16.6

* According to an International Atomic Energy Agency map, 1989.
† A total of 26 children (3.9%) lived in very high contaminated areas (15–40 Ci/km²).

Bar Joseph et al. 2004. Epidemiology

Historical exposures



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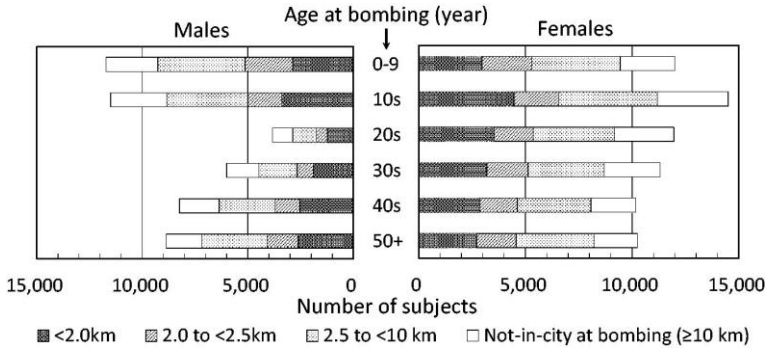

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Bar Joseph et al. 2004. Epidemiology

→ No significant effect on cognition among A-bomb survivors & exposed children after Chernobyl accident

Childhood CT scans

Head CT scans
<10 yrs at exposure

First 10 years post-exposure

50 mGy → risk for leukemia **x3**
60 mGy → risk for brain cancer **x3**

Pearce. Lancet. 2012

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Absolute risk

1 excess case of leukaemia/brain tumor per 10 000 head CT scans

Pearce. Lancet. 2012

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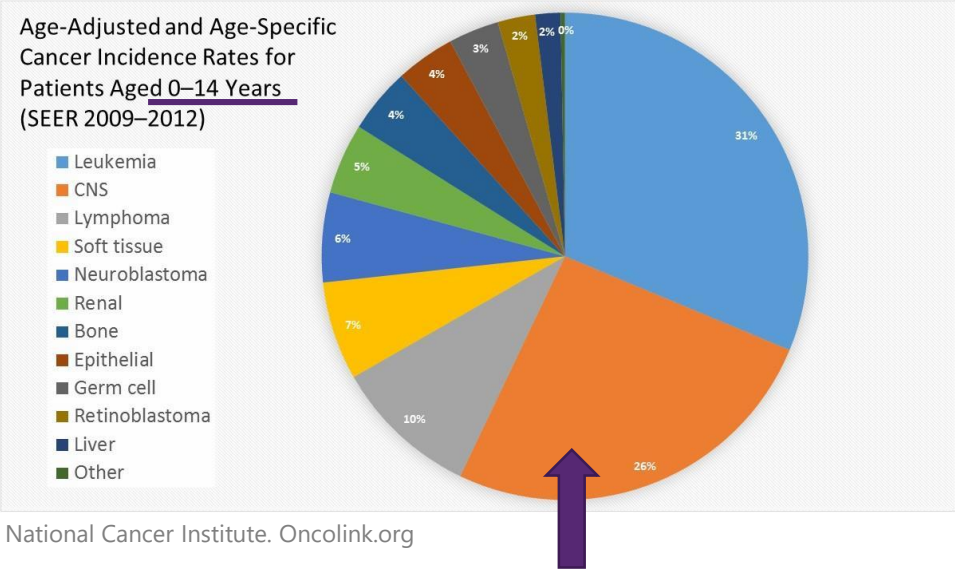
Absolute risk
1 excess case of leukaemia/brain tumor per 10 000 head CT scans

- Clinical benefits should outweigh the small absolute risks
- Alternative procedures should be considered if appropriate

Pearce. Lancet. 2012

Childhood CNS cancer & survival rates



National Cancer Institute. Oncolink.org

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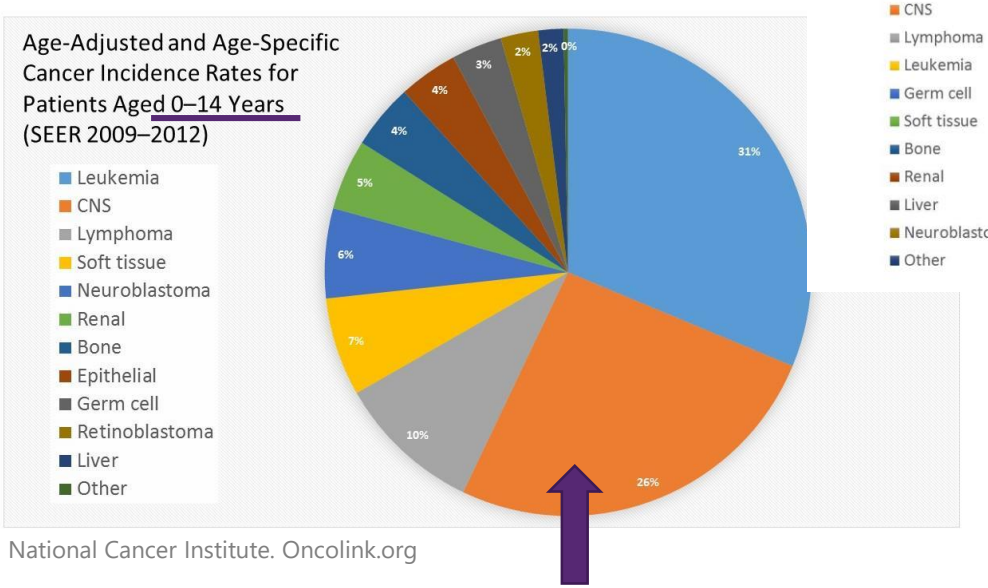

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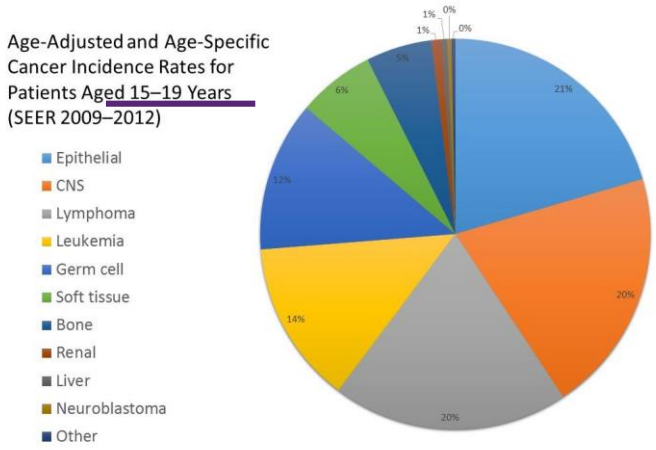

https://www.survivorvision.org/stats.html

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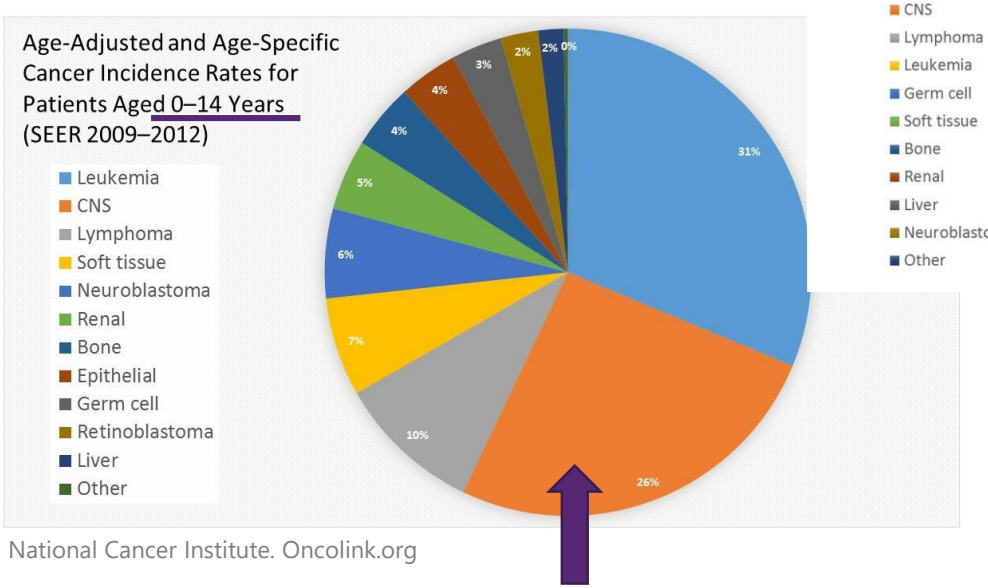

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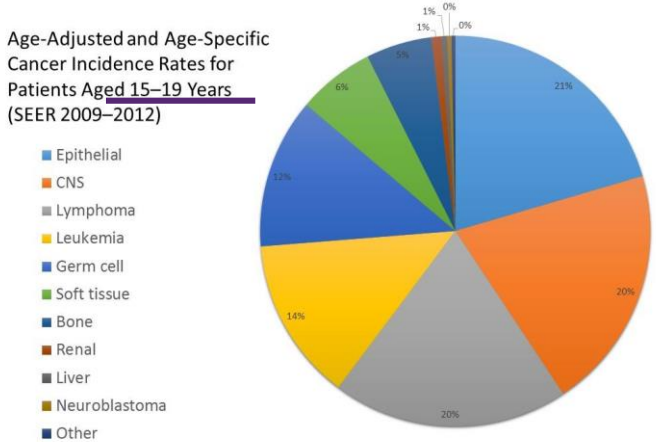
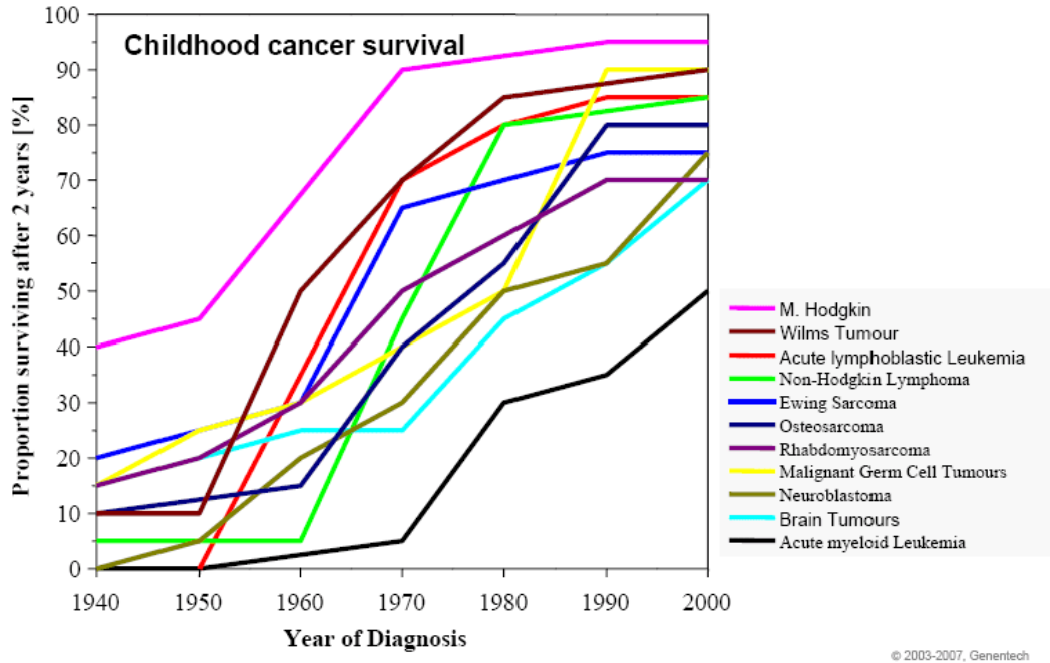


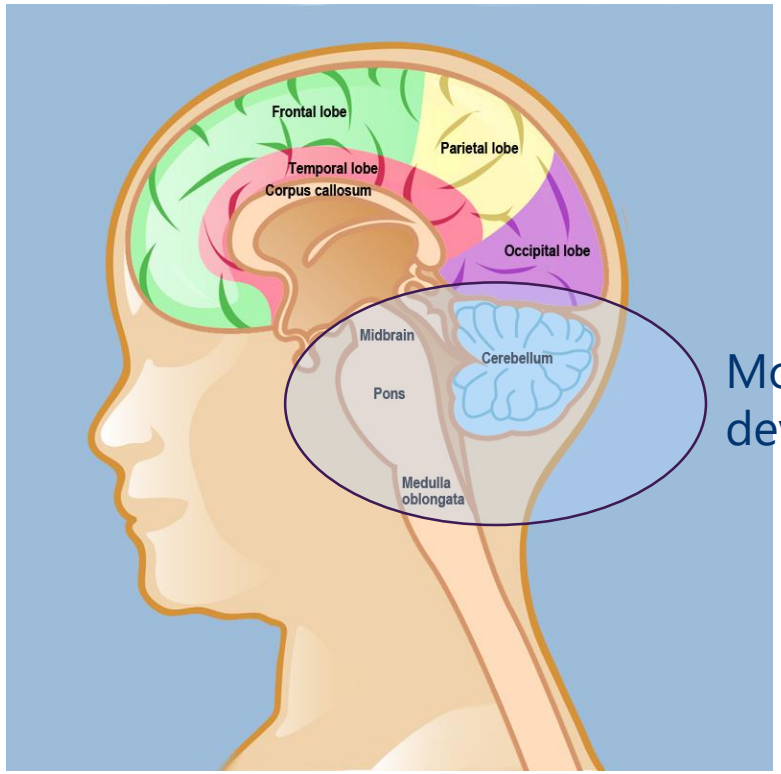


https://www.survivorvision.org/stats.html

© 2003-2007, Genentech

SCK: Restricted

Type of tumors & cognitive impairment

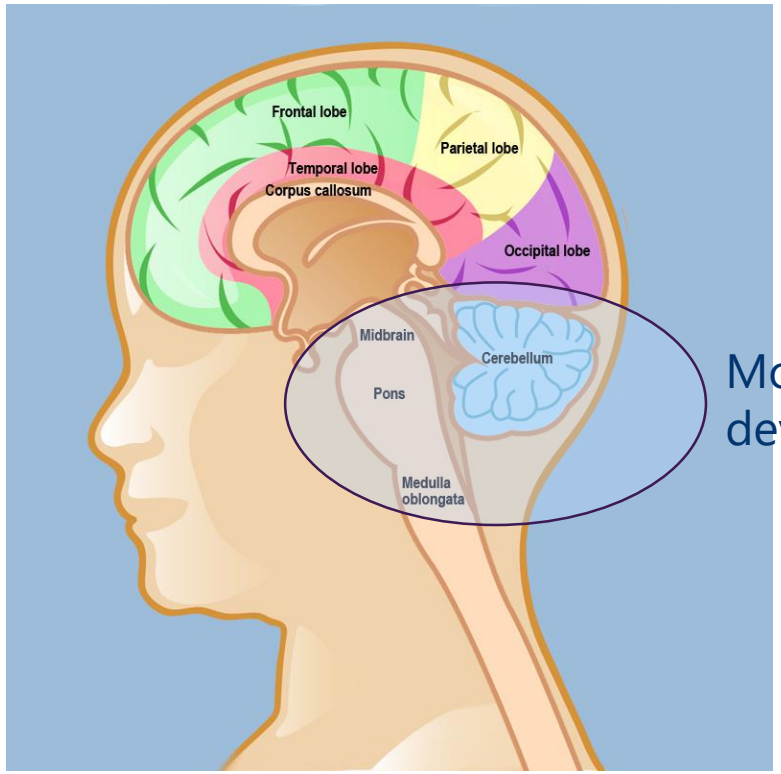


Most common sites of tumor development in children

- Medulloblastoma
- Astrocytoma
- Glioma

Kirsch & Tarbell. The Oncologist. 2004

Type of tumors & cognitive impairment



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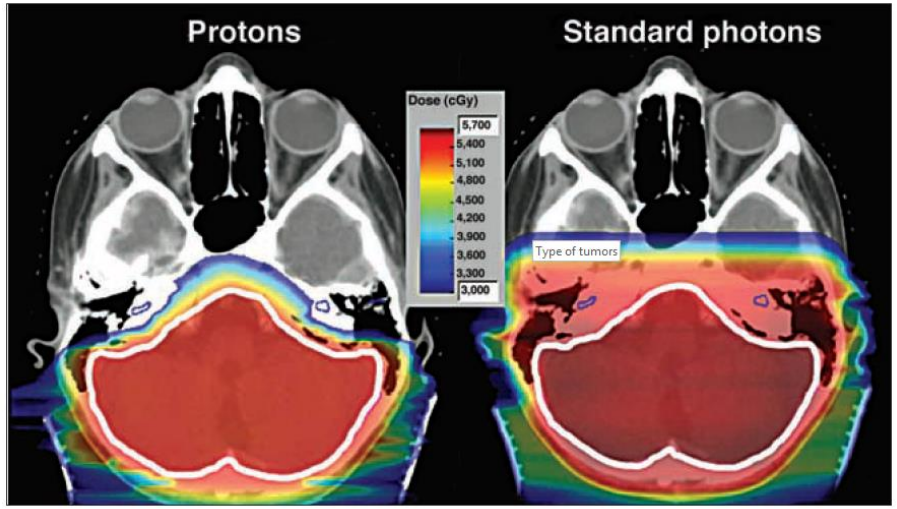
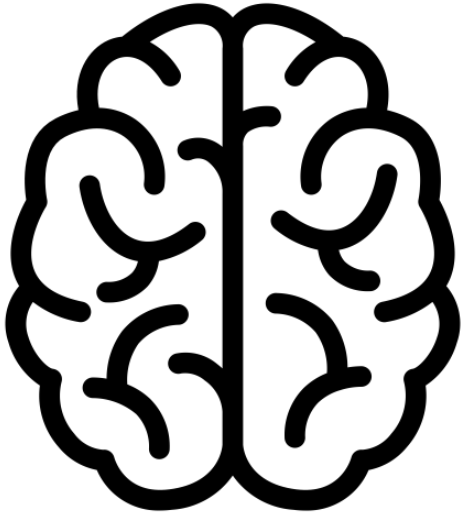


Kirsch & Tarbell. The Oncologist. 2004

Type of tumors & cognitive impairment

Executive function

Processing speed

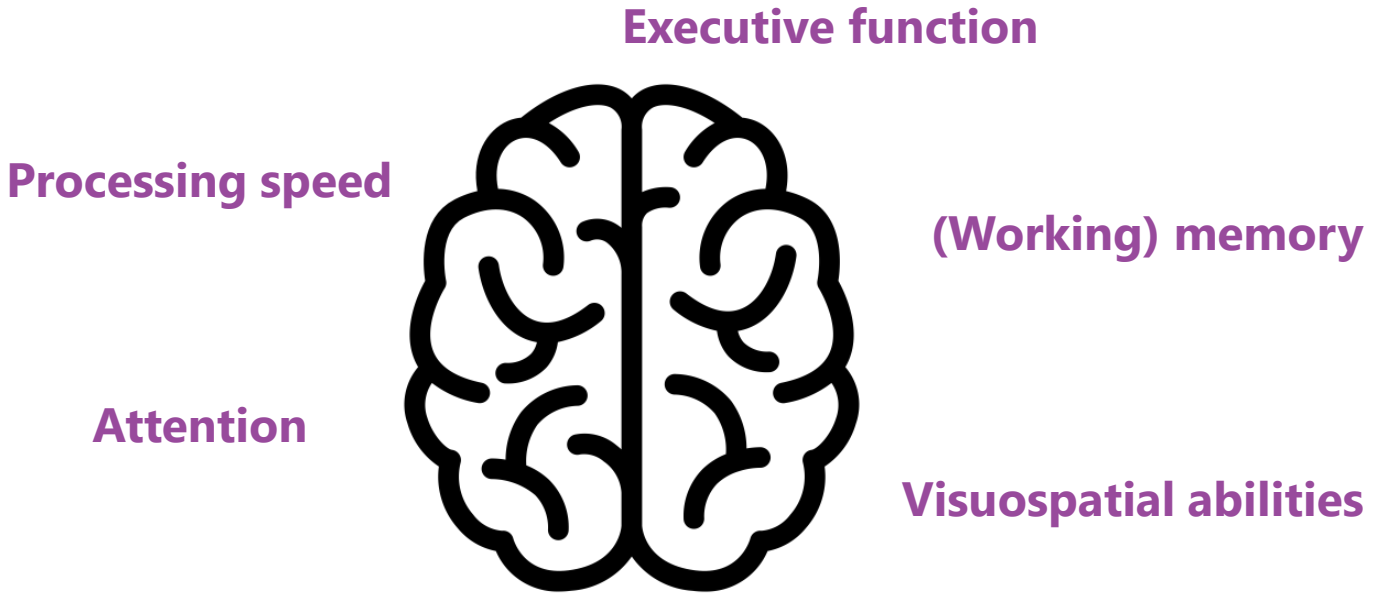


(Working) memory

Attention

Visuospatial abilities

Type of tumors & cognitive impairment



- Greater after radiation than in children undergoing surgery and/or chemotherapy
- Still occurring in absence of radiation treatment (attention deficits)
- Younger age at diagnosis associated with poorer outcomes

Some examples

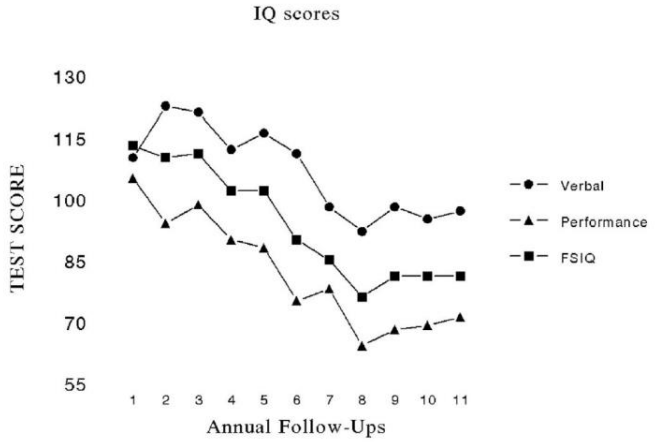
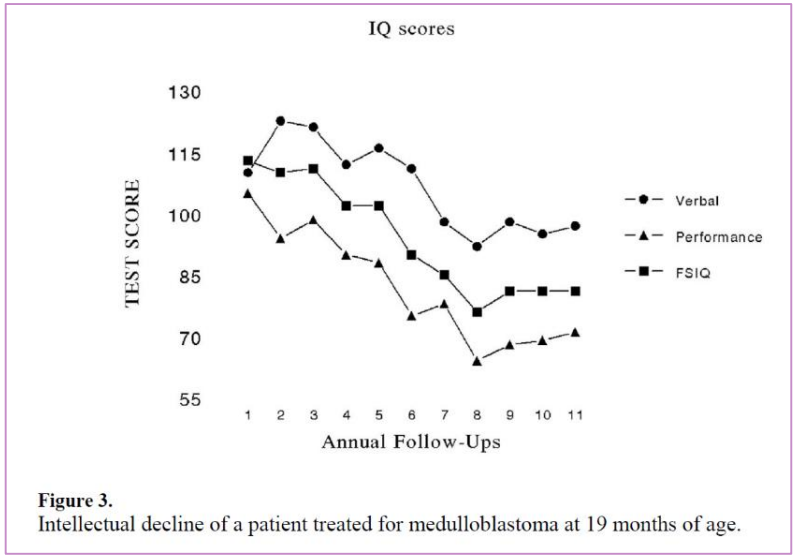


Figure 3.
Intellectual decline of a patient treated for medulloblastoma at 19 months of age.

Askins and Moore, J Child neurol. 2008

Some examples



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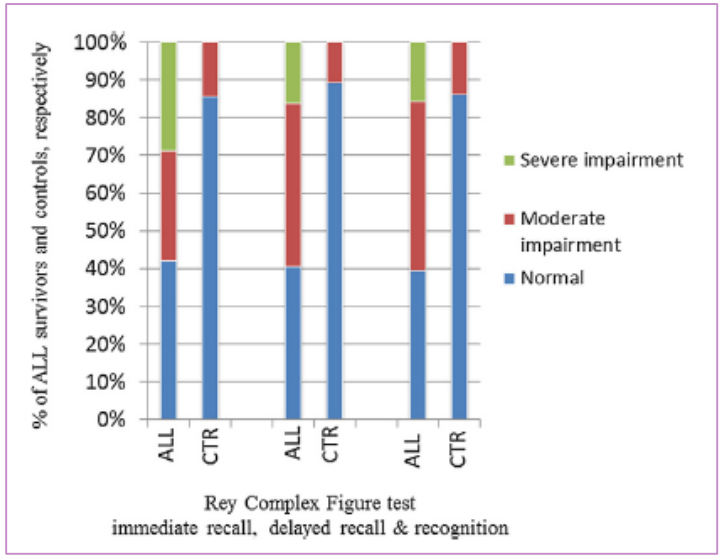

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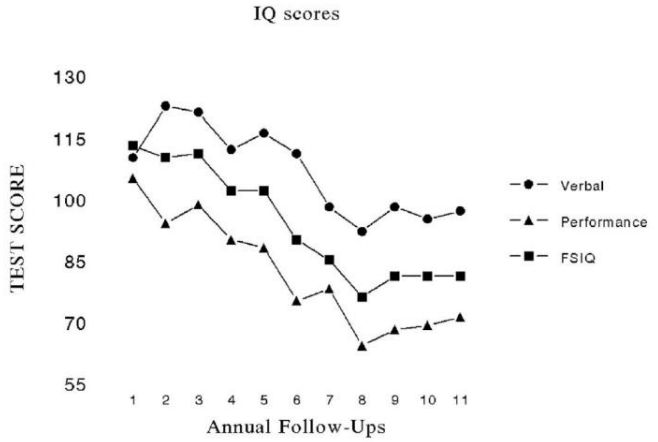

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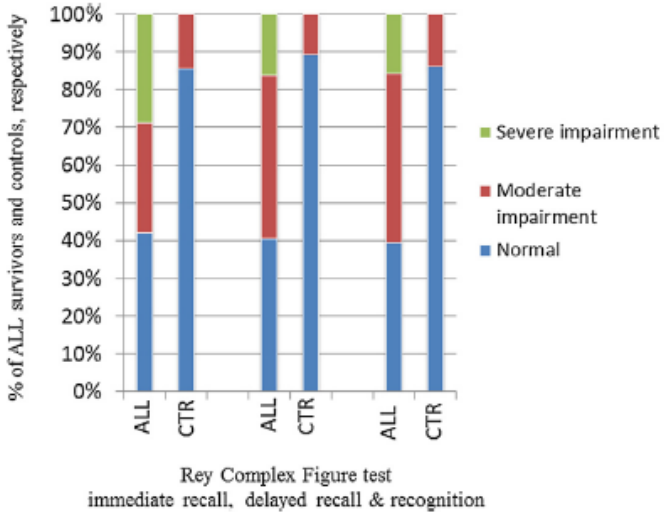

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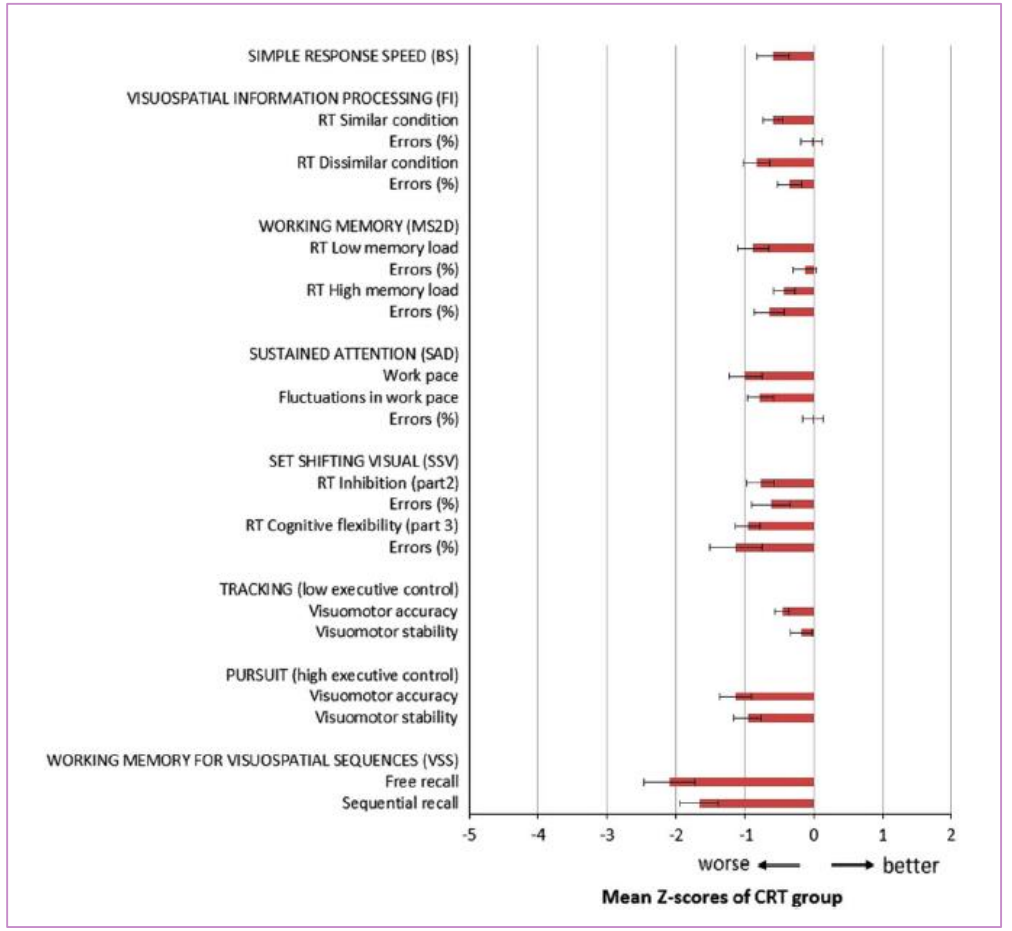
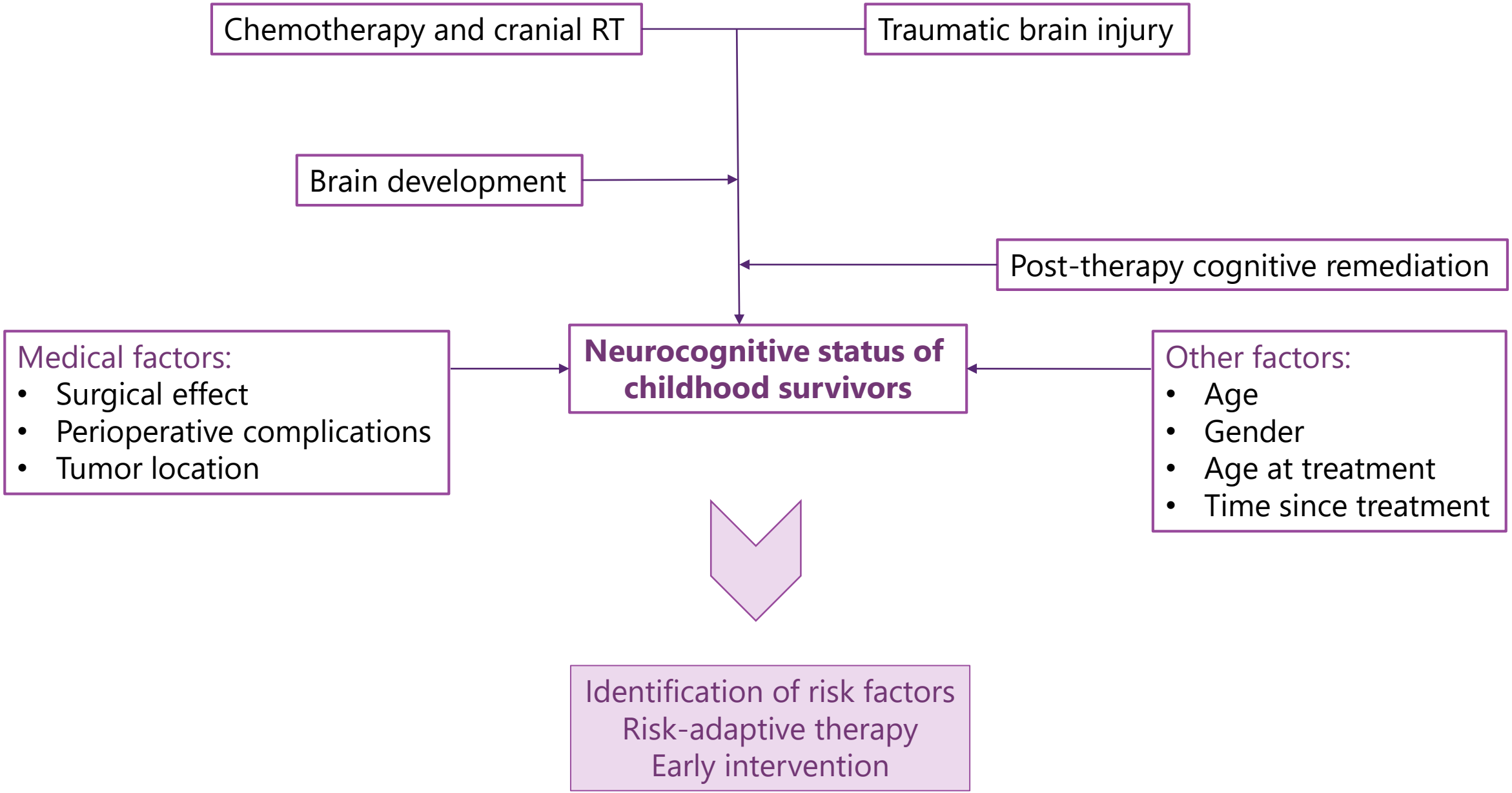


Schuitema et al. J intern Neuropsychol Society. 2015



Adapted from Askins and Moore, J Child neurol, 2008

A link with brain aging?

Table 3 Frequency (%) of participants classified with possible dementia and MCI by cognitive deficit criterion

	≥ 1.5 SD on one or more test	≥ 2.0 SD on one or more test	≥ 1.5 SD on two or more tests
No impairment	46 (23%)	62 (31%)	75 (38%)
MCI	131 (66%)	116 (59%)	103 (52%)
A, SD	17 (13%)	19 (16%)	10 (10%)
A, MD	76 (58%)	55 (47%)	76 (74%)
NA, SD	25 (19%)	28 (24%)	4 (4%)
NA, MD	13 (10%)	14 (12%)	13 (13%)
Possible dementia	20 (10%)	19 (10%)	19 (10%)

Subtype percentages are conditional on having MCI

A Amnestic, *NA* non-amnestic, *MD* multiple domains, *SD* single domain

Cramer et al. Journal of Neuro-Oncology. 2018

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Cramer et al. Journal of Neuro-Oncology. 2018

- Adult brain tumor patients
- NIA-AA criteria for Mild Cognitive Impairment Syndrome
- What about childhood survivors?

A link with brain aging?

Evaluation of Memory Impairment in Aging Adult Survivors of Childhood Acute Lymphoblastic Leukemia Treated With Cranial Radiotherapy

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- Impaired immediate and delayed memory
- Thinning of brain volumes, e.g. temporal lobe
- Lower hippocampal volumes
- Reduced overall cognitive status
- Dose-response effect

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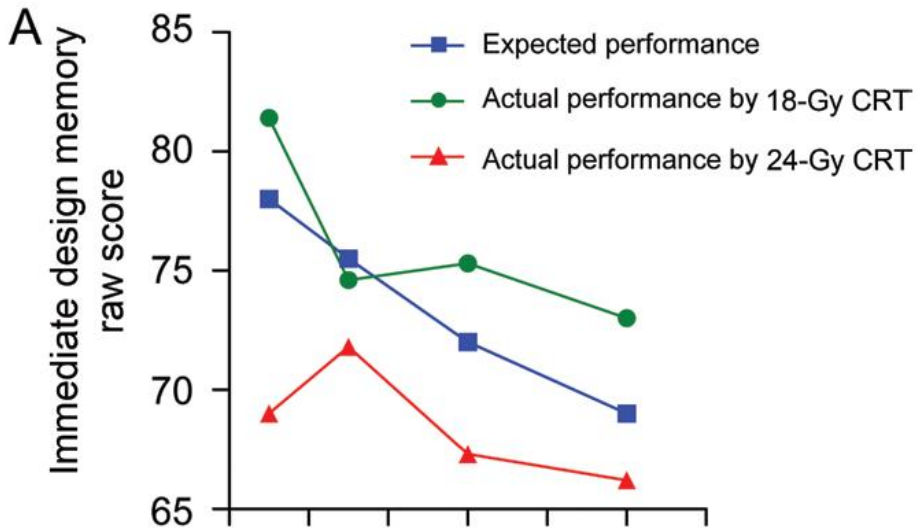

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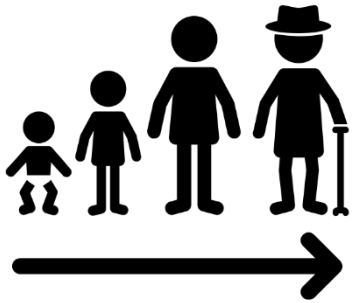
Journal of the National Cancer Institute. 2013

Consistent with **early aging & mild cognitive impairment**



- Impaired immediate and delayed memory
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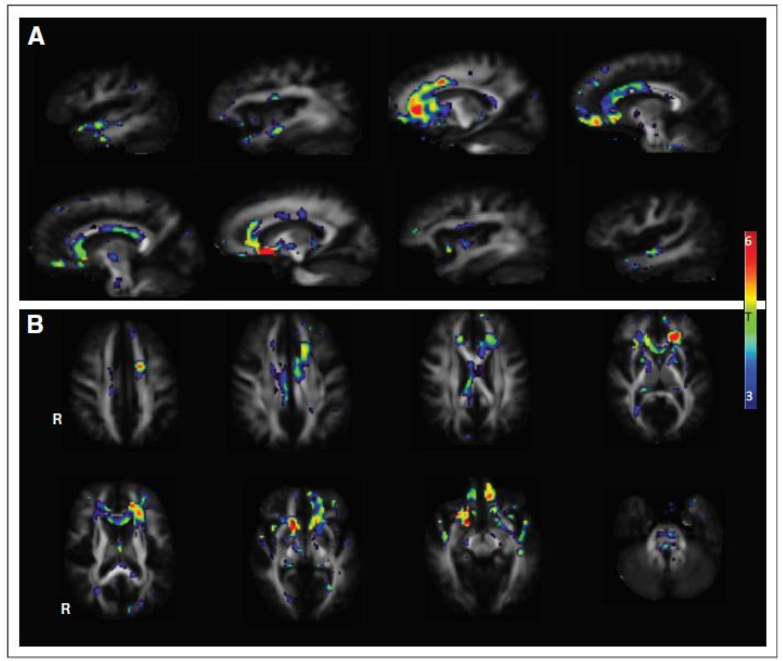
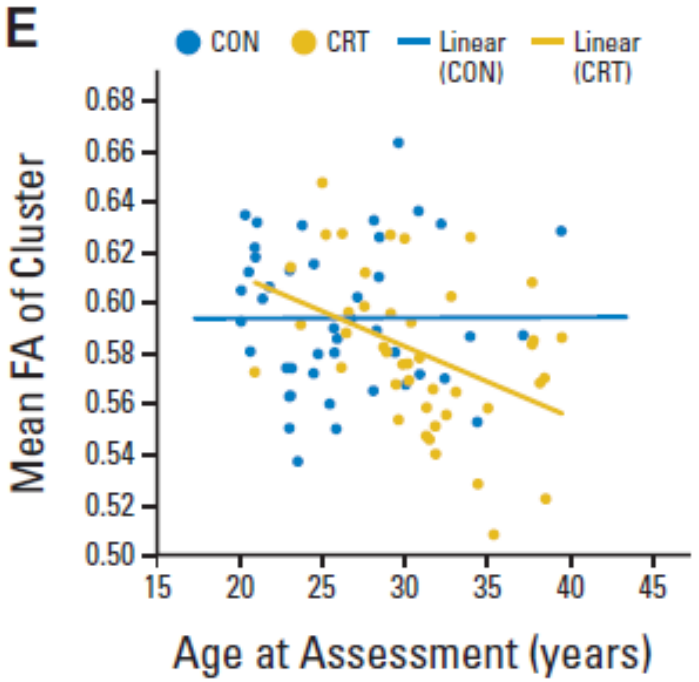
For certain delayed memory domains, a **cognitive age** two and three decades beyond their chronological age was estimated

A link with brain aging?

- Link with decline in FA, most importantly in the frontal and parietal white matter, accelerated aging & neuropsychological dysfunction
- Anatomic similarities between childhood ALL survivors 25 years post-treatment and AD patients





Schuitema et al. J Clinic Oncol. 2013

How to prevent late side-effects?

- Advanced radiotherapy techniques
- Early intervention
- Hospital school programs
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Survivors of childhood ALL and brain tumor patients & adult brain tumor patients

Assessment of cognitive skills, attention, sociability,…

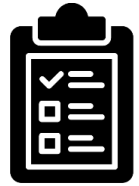

Table 1 A summary of the evidence regarding the potential benefit of pharmacologic intervention in cancer patients with cognitive impairment and fatigue

Medication	Mechanism of action	Evidence of impact on cognition in cancer patients
MODAFINIL	Thought to inhibit GABA outflow tracts within the ventro-lateral preoptic area of the hypothalamus.	Clinical trials have looked at fatigue as a primary outcome and cognition as a secondary one, although most have demonstrated efficacy in improving cognition.
METHYLPHENIDATE	Dopaminergic and noradrenergic agonist which acts to increase levels of these neurotransmitters within the frontal striatal network.	Randomised, double-blind trials in childhood cancer patients suggest efficacy, but no evidence of superiority over placebo in adult trials.
DONEPEZIL	Centrally acting anticholinergic used in the management of Alzheimer's Disease.	Open-label Phase II studies in glioma patients suggested statistically significant improvement in cognitive functioning.
LITHIUM	Cation with an unknown mechanism of action used in the management of bipolar mood disorder.	Murine models and efficacy data from bipolar patients suggest anti-apoptotic and neuroprotective potential.
PPARs	Nuclear hormone receptor functioning as a transcription factor, targeted in the control of type II diabetes mellitus.	Murine models have demonstrated protection against radiation induced cognitive dysfunction.
ARBs	Antagonism of the angiotensin II receptor used in the management of hypertension.	Murine models have demonstrated protection against radiation induced cognitive dysfunction.
NOS	Produces NO which functions as a neurotransmitter.	None, theoretical benefit through induction of NOS and subsequent antioxidant activities.
MEMANTINE	NMDA antagonist used in the management of Alzheimer's Disease.	Recent randomised placebo-controlled double-blind trial in patients receiving whole brain radiation showed longer time to cognitive decline over placebo.
N-ACETYL CYSTEINE	Provides cysteine, the rate limiting step in the synthesis of the anti-oxidant glutathione.	Limited evidence of efficacy in Phase II trials in Alzheimer's patients.
RESVERATROL	Unknown, demonstrates anti-apoptotic and anti-oxidant properties within cell cultures.	Phase II studies in Alzheimer's patients suggest little to no cognitive benefit.
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NOS	Produces NO which functions as a neurotransmitter.	None, theoretical benefit through induction of NOS and subsequent antioxidant activities.
MEMANTINE	NMDA antagonist used in the management of Alzheimer's Disease.	Recent randomised placebo-controlled double-blind trial in patients receiving whole brain radiation showed longer time to cognitive decline over placebo.
N-ACETYL CYSTEINE	Provides cysteine, the rate limiting step in the synthesis of the anti-oxidant glutathione.	Limited evidence of efficacy in Phase II trials in Alzheimer's patients.
RESVERATROL	Unknown, demonstrates anti-apoptotic and anti-oxidant properties within cell cultures.	Phase II studies in Alzheimer's patients suggest little to no cognitive benefit.
NSAIDS	Inhibition of COX isoforms.	Recent Cochrane review indicates no significant impact in slowing cognitive decline in Alzheimer's patients, Women's Health study subanalysis echoes this finding.

Table 1 A summary of the evidence regarding the potential benefit of pharmacologic intervention in cancer patients with cognitive impairment and fatigue

Medication	Mechanism of action	Evidence of impact on cognition in cancer patients
MODAFINIL	Thought to inhibit GABA outflow tracts within the ventro-lateral preoptic area of the hypothalamus.	Clinical trials have looked at fatigue as a primary outcome and cognition as a secondary one, although most have demonstrated efficacy in improving cognition.
METHYLPHENIDATE	Dopaminergic and noradrenergic agonist which acts to increase levels of these neurotransmitters within the frontal striatal network.	Randomised, double-blind trials in childhood cancer patients suggest efficacy, but no evidence of superiority over placebo in adult trials.
DONEPEZIL	Centrally acting anticholinergic used in the management of Alzheimer's Disease.	Open-label Phase II studies in glioma patients suggested statistically significant improvement in cognitive functioning.
LITHIUM	Cation with an unknown mechanism of action used in the management of bipolar mood disorder.	Murine models and efficacy data from bipolar patients suggest anti-apoptotic and neuroprotective potential.
PPARs	Nuclear hormone receptor functioning as a transcription factor, targeted in the control of type II diabetes mellitus.	Murine models have demonstrated protection against radiation induced cognitive dysfunction.
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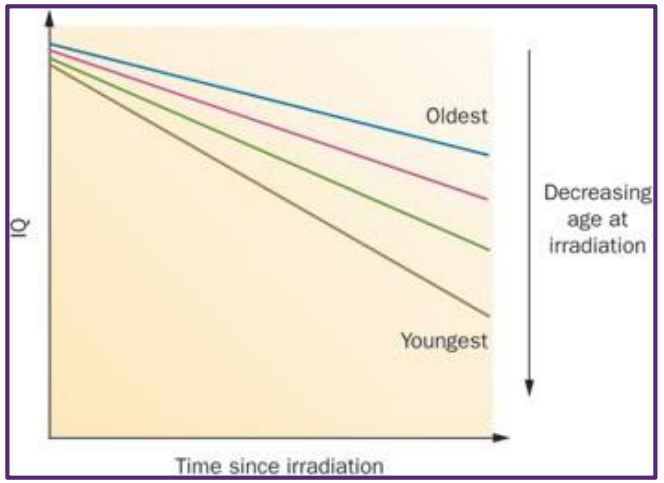
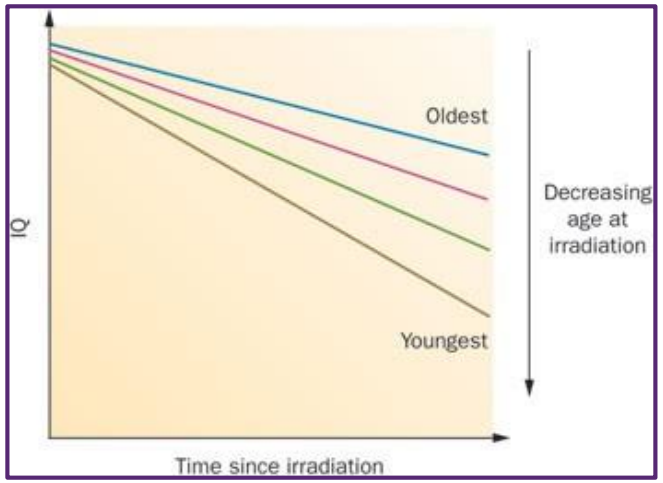
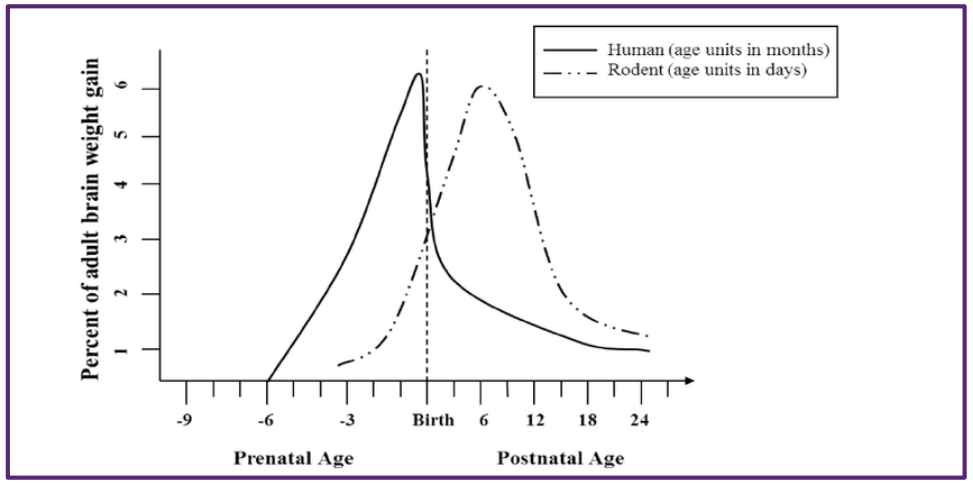
Experimental data

Sensitivity of the developing brain



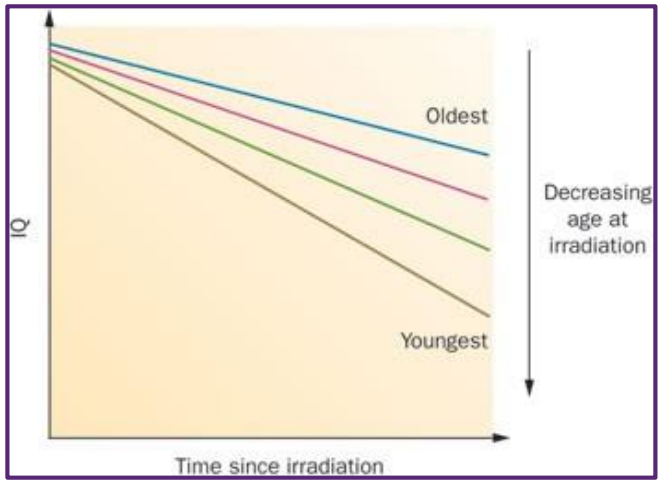
Sensitivity of the developing brain

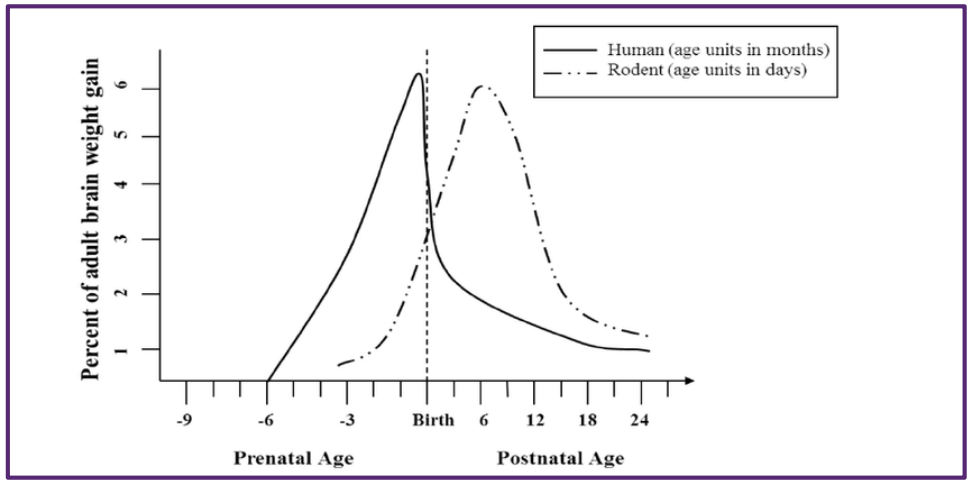




Brain growth spurt

Sensitivity of the developing brain





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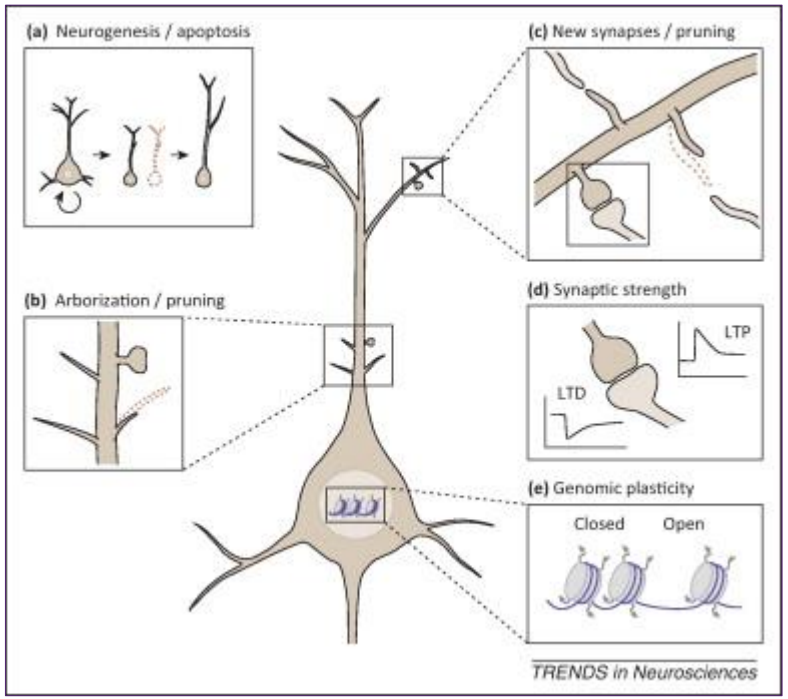
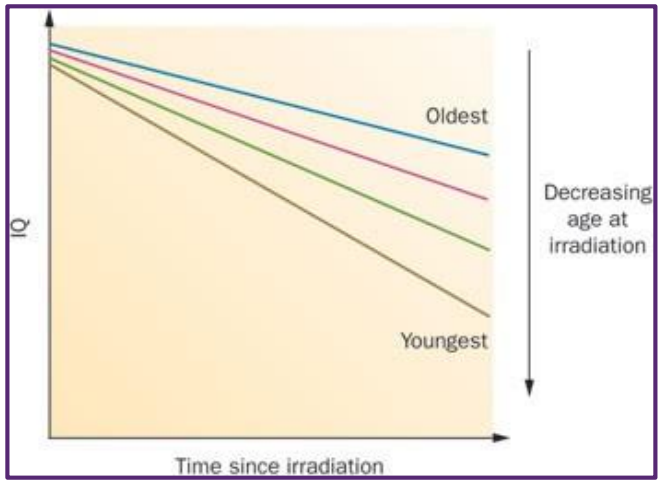
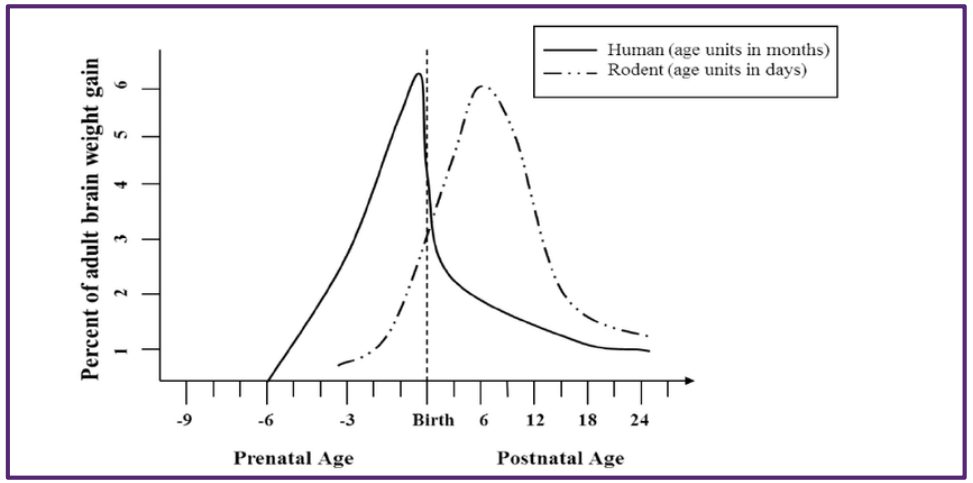


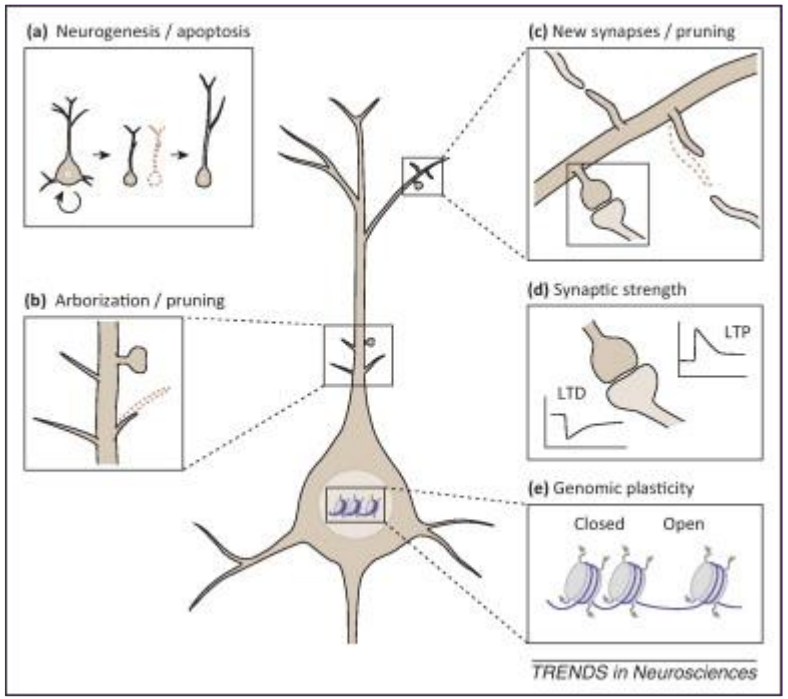
Castrén & Hen. Trends in Neurosciences. 2013

- Synaptogenesis & synaptic pruning

Sensitivity of the developing brain

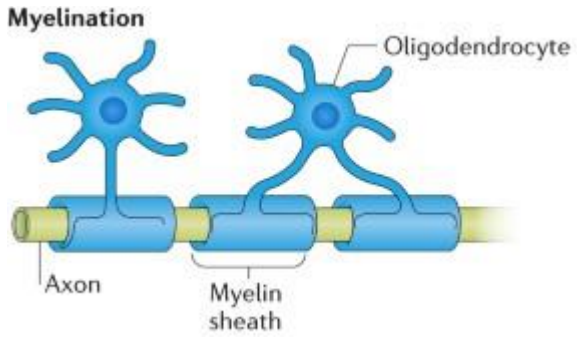






Castrén & Hen. Trends in Neurosciences. 2013

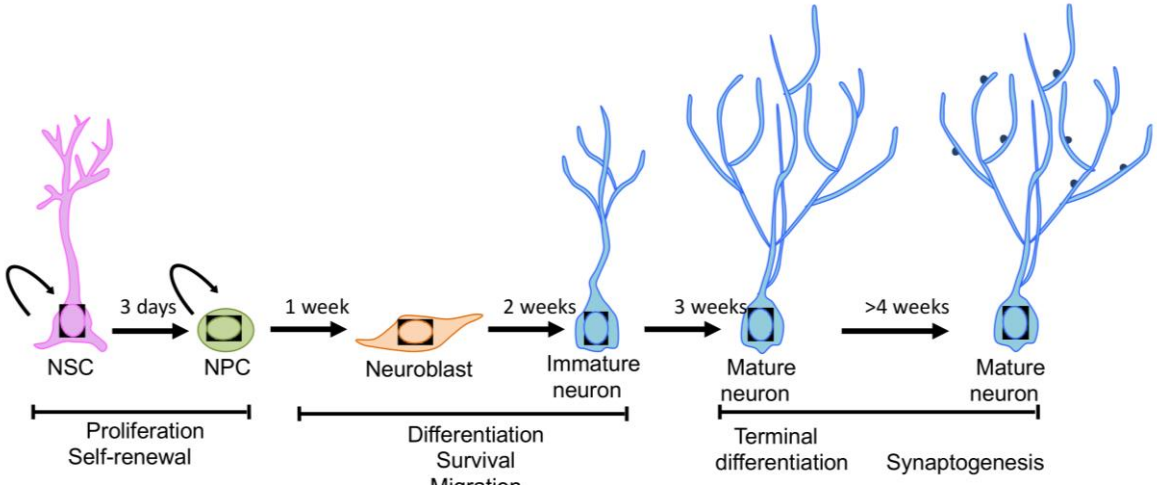
Brain growth spurt

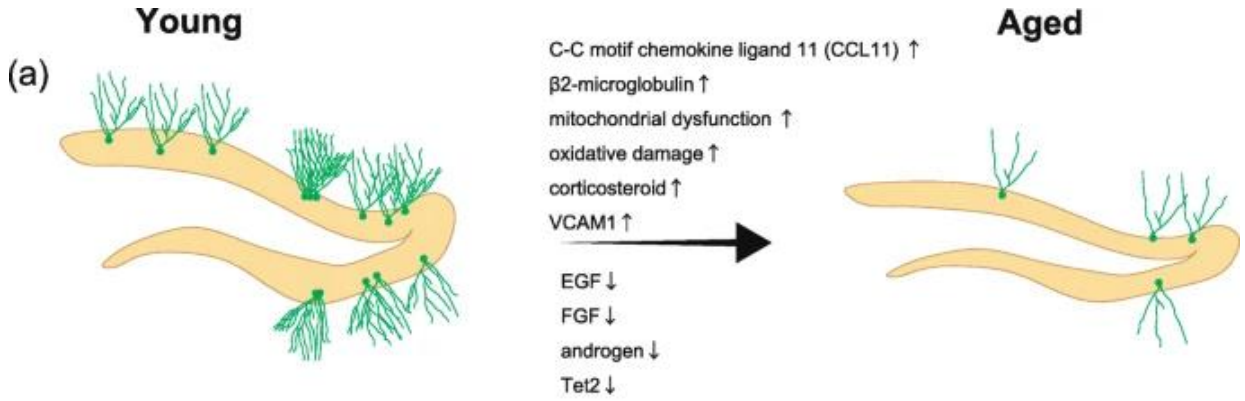


- Synaptogenesis & synaptic pruning
- Replication of glial cells
- Myelination (development of white matter)

Sensitivity of the developing brain

High degree of neurogenesis





Niklison-Chirou. Int J Mol Sci. 2020

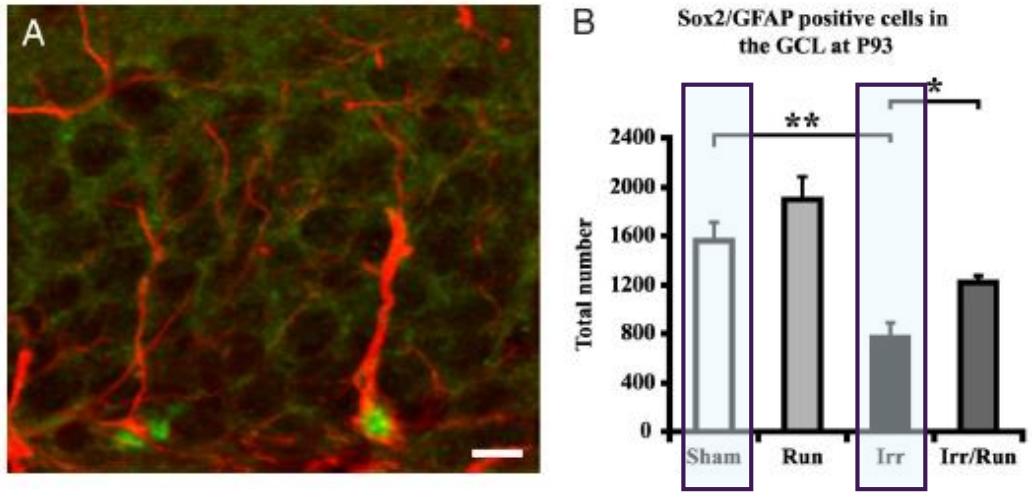
Kase et al. Inflammation and Regeneration. 2020

Some examples

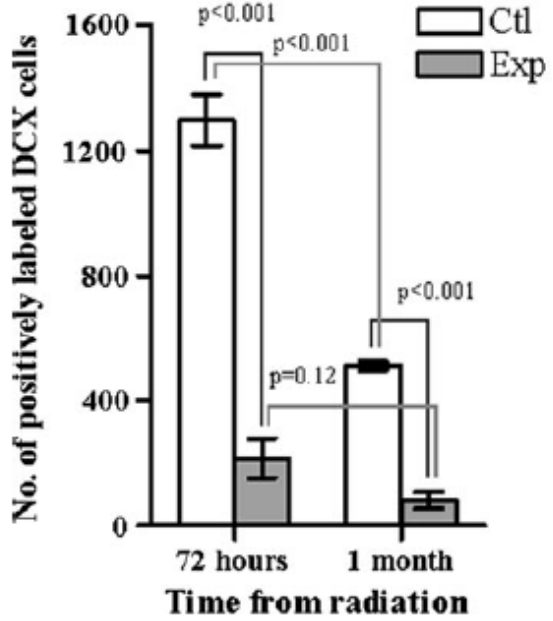
Some examples

Reduced neurogenesis

Some examples



Reduced neurogenesis



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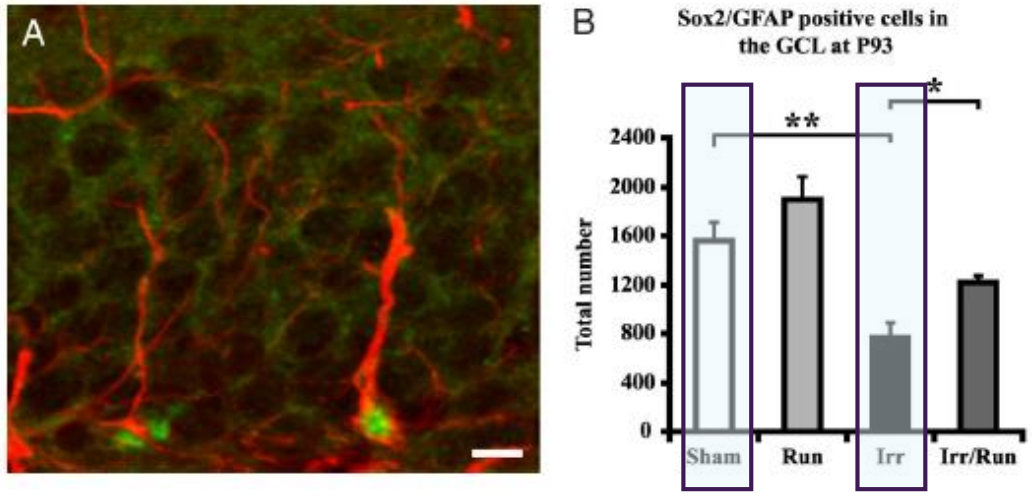
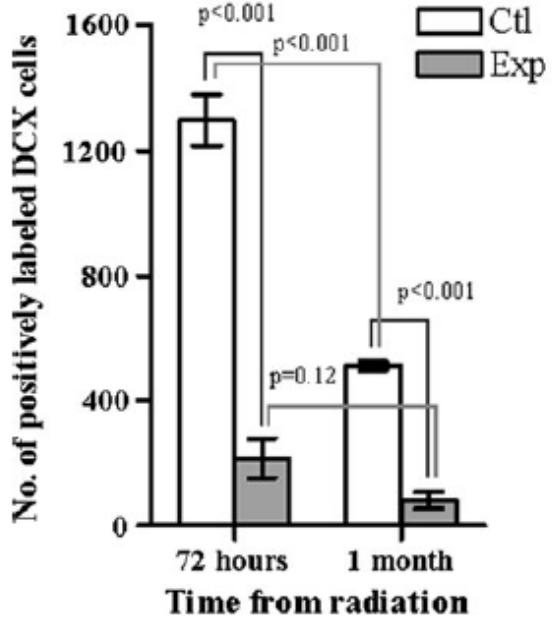
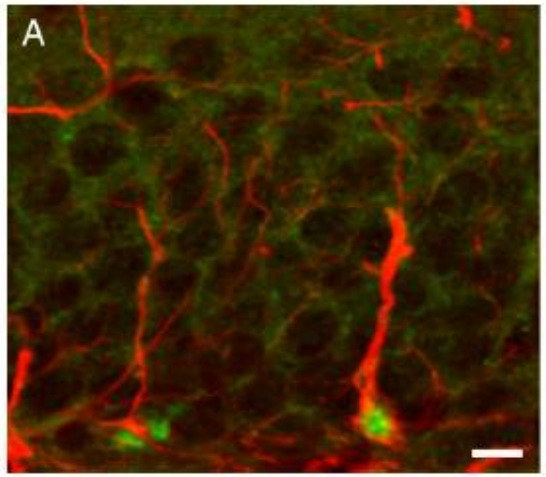


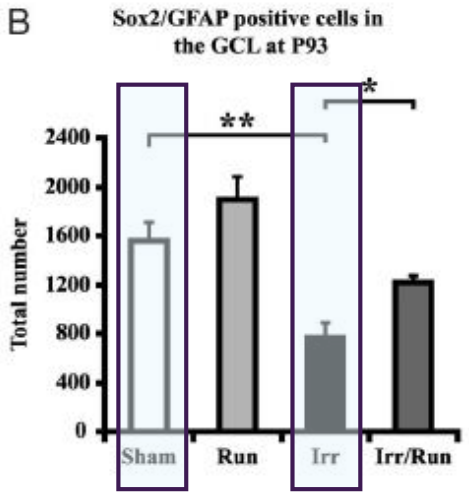
Reduced neurogenesis

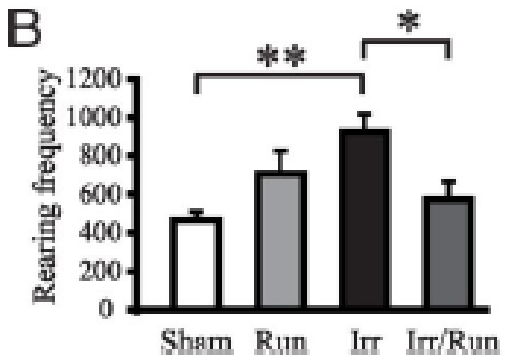


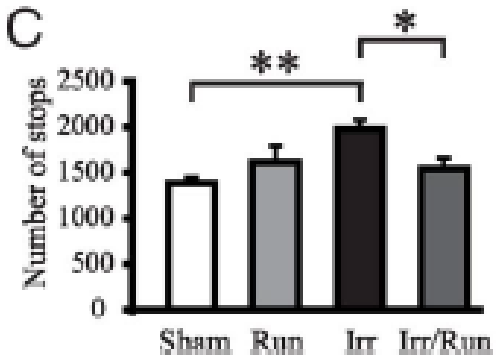
Altered general behavior & novel object recognition

Some examples

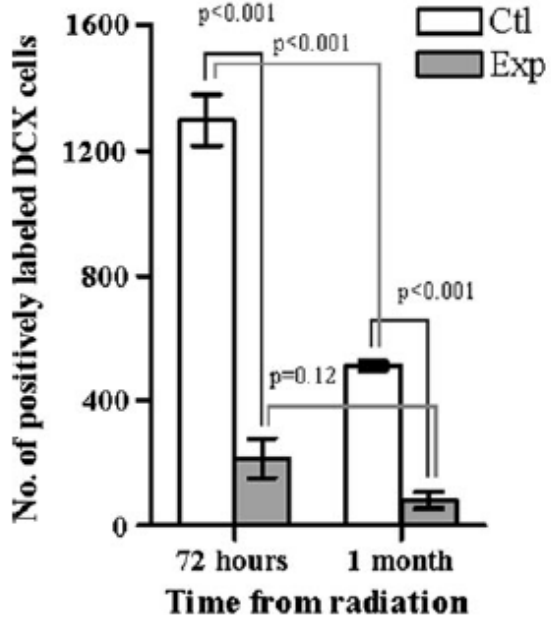




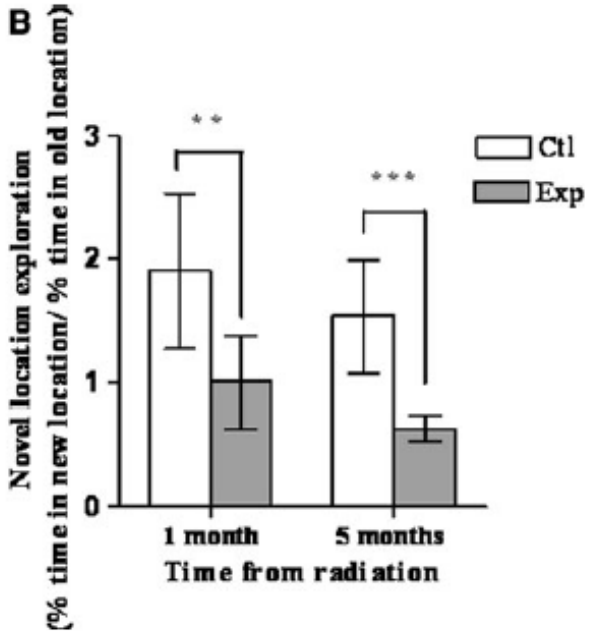




Reduced neurogenesis



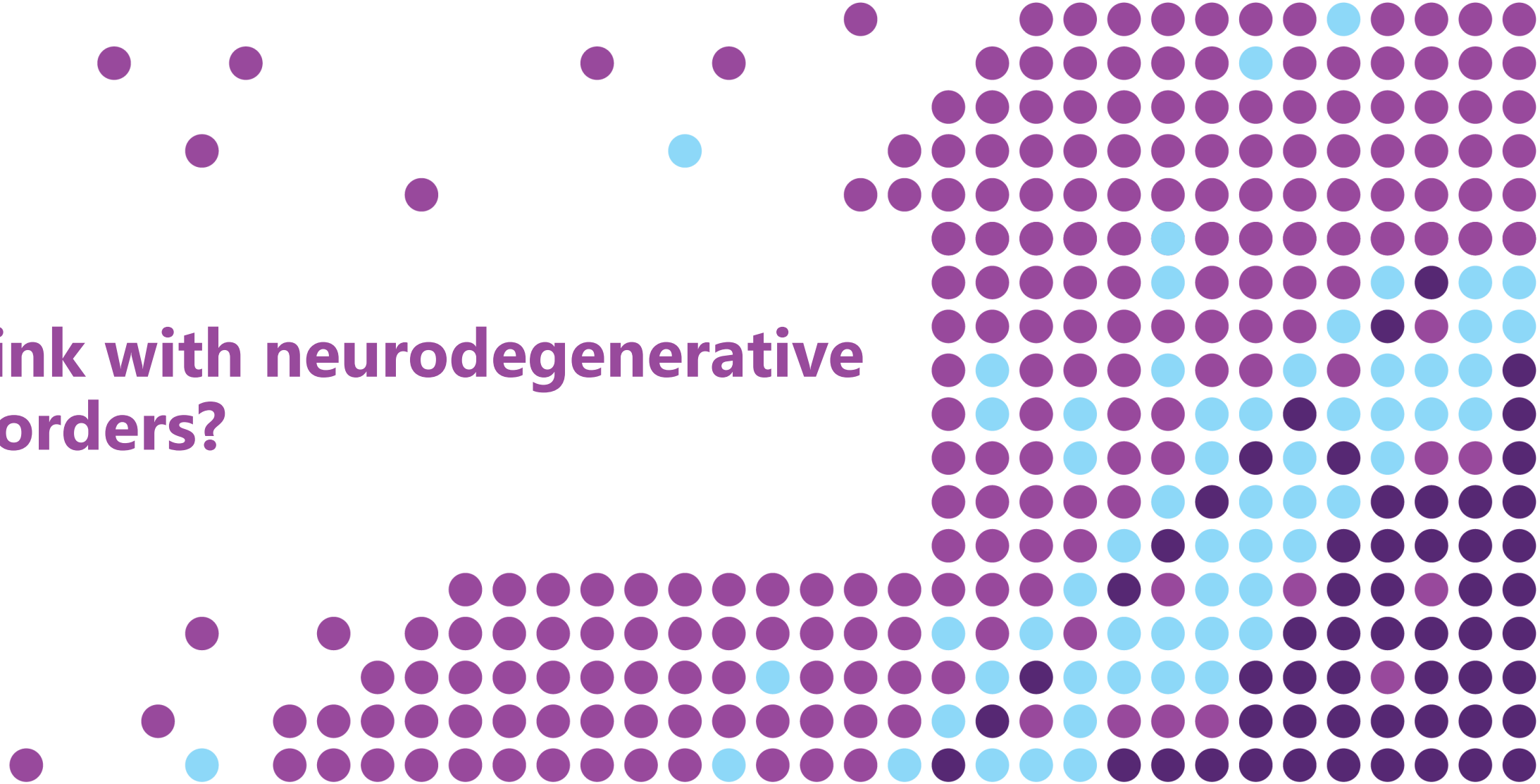
Altered general behavior & novel object recognition



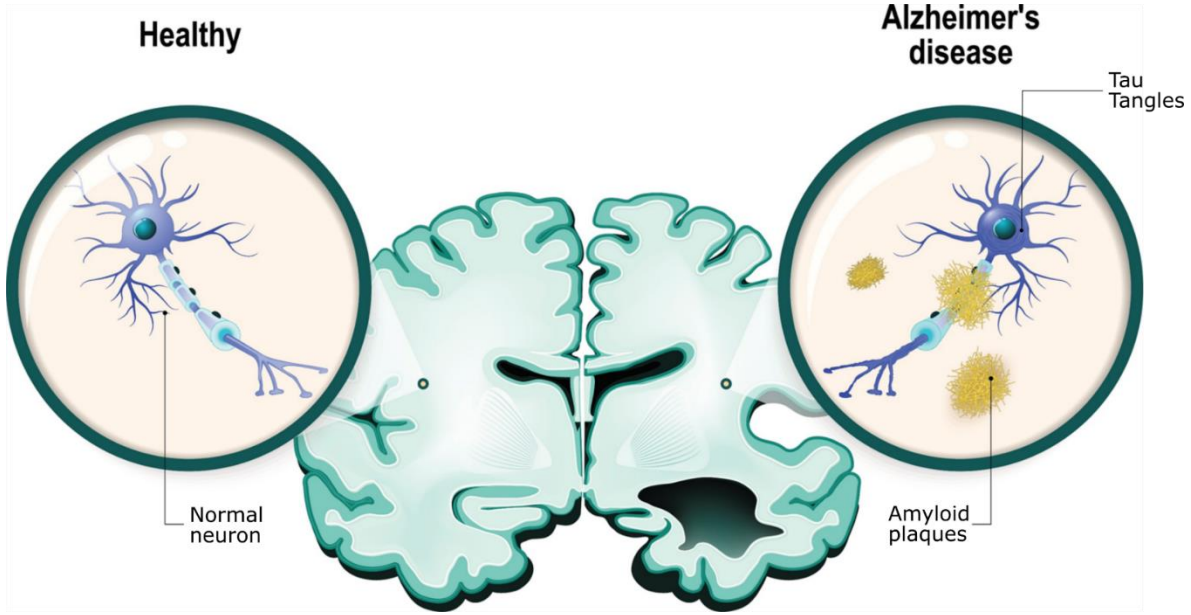
Naylor et al. PNAS. 2008

Rao et al. J Neurooncol.2011

A link with neurodegenerative disorders?



Radiation & Alzheimer's – Is there a link?



OHSU Brain Institute 2020

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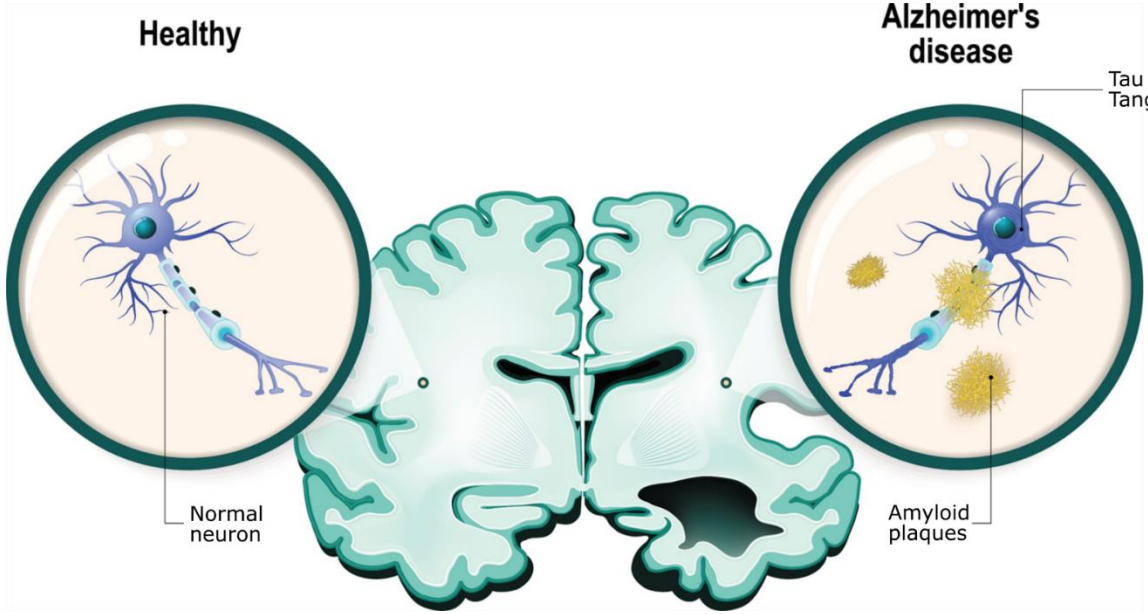

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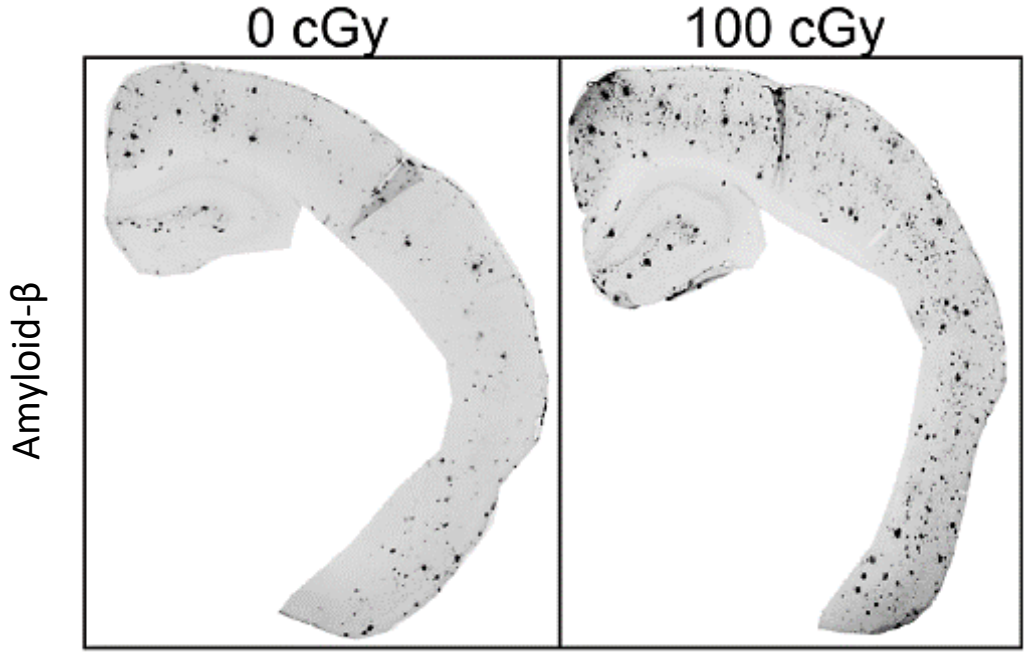
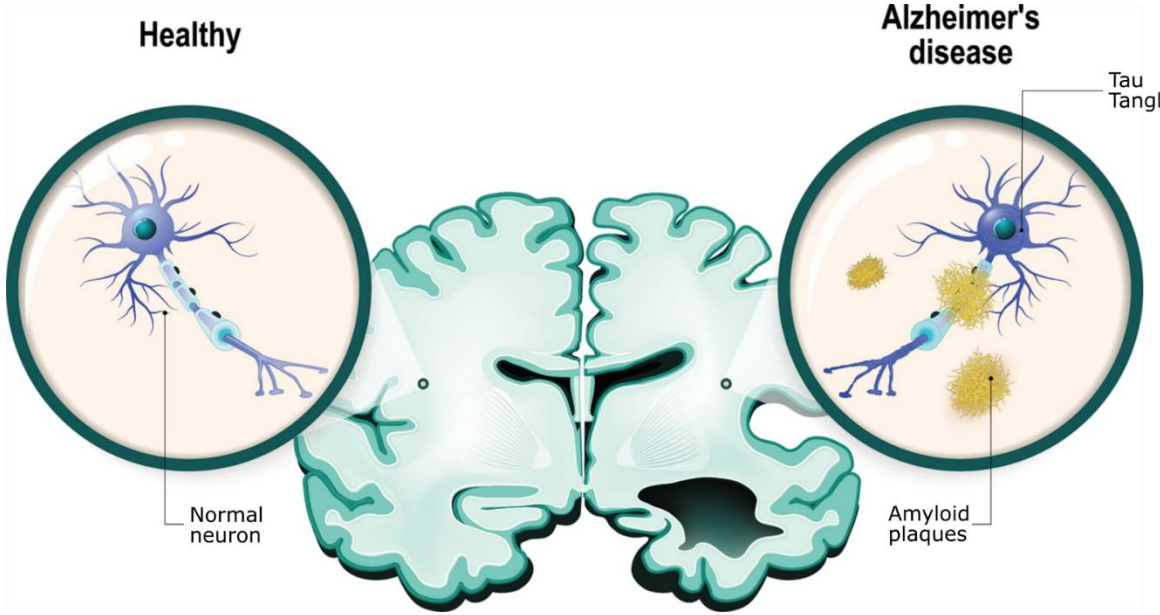


Cherry et al. *Plos One* 2012

Radiation & Alzheimer's – Is there a link?



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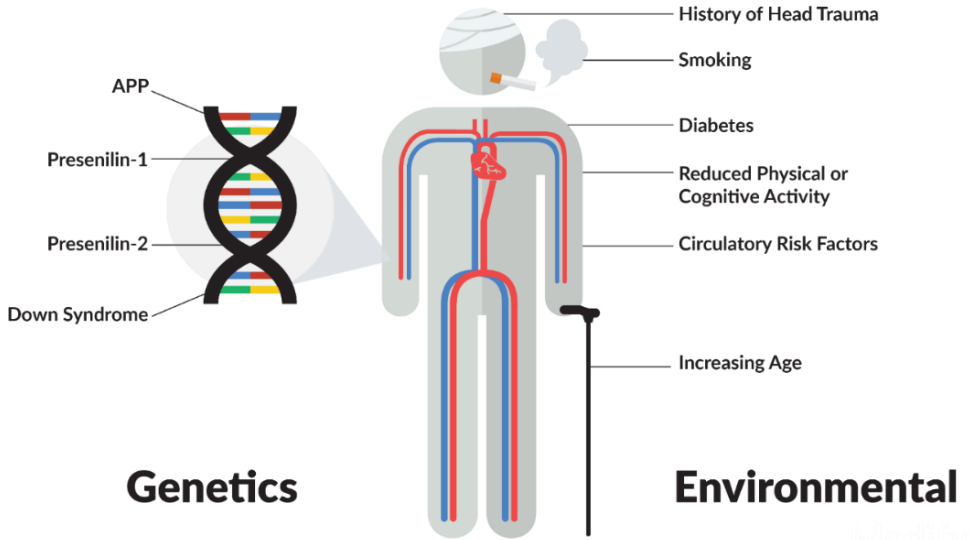

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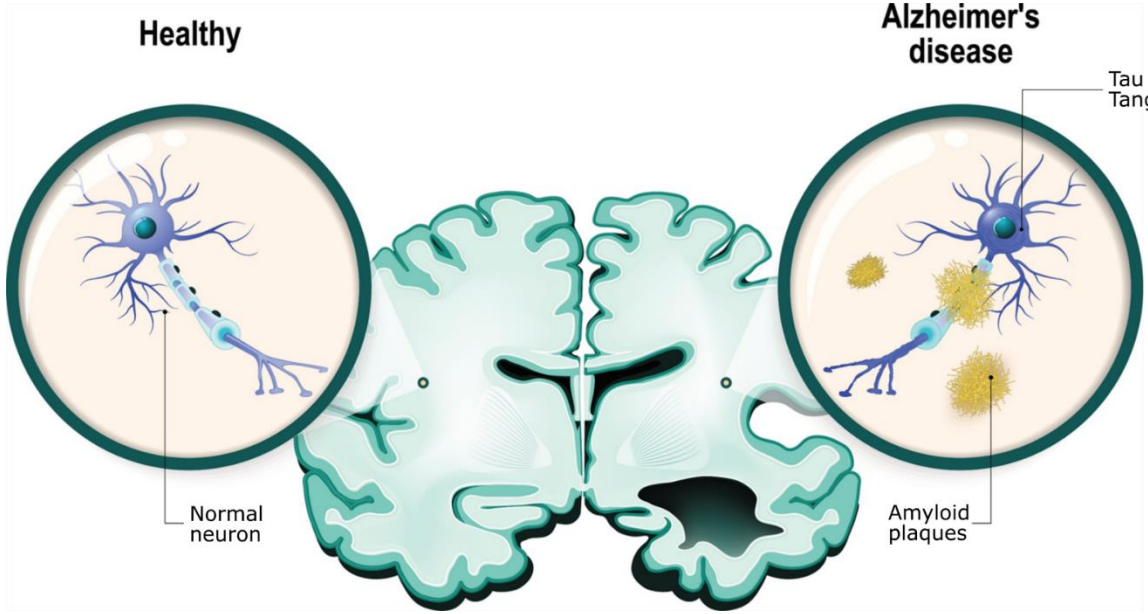

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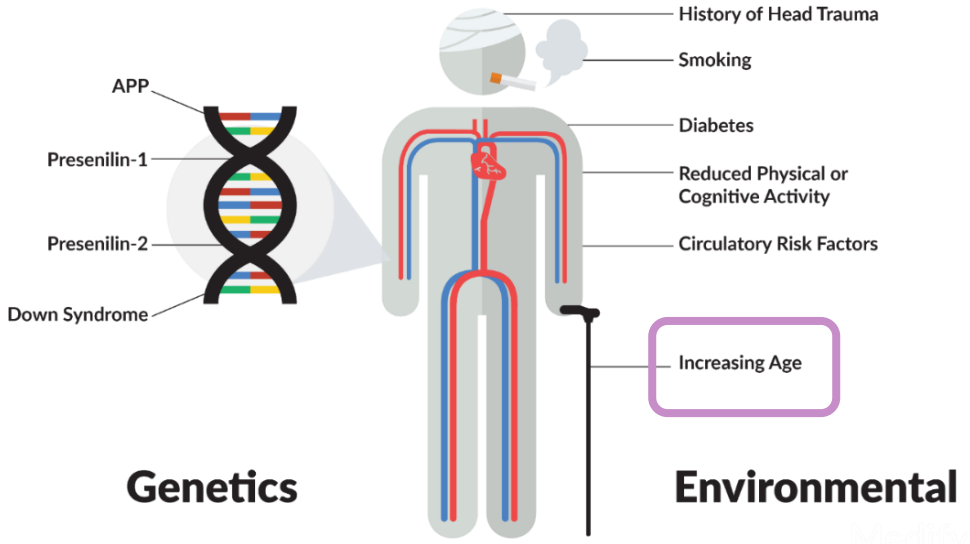
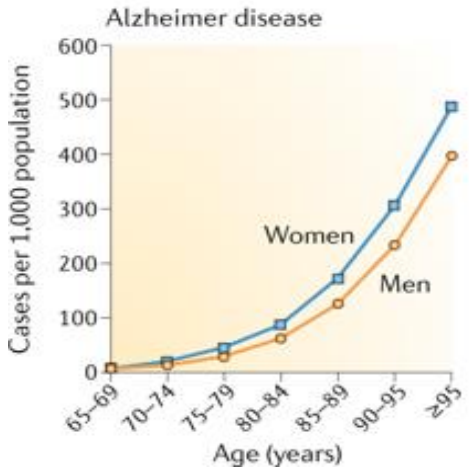




Hou et al., Nature Reviews Neurology, 2019

3xTg AD mice

Female

Early effects

DNA damage

Oxidative stress

DNA damage & oxidative stress

Neurogenesis

Behavior

Plasticity

AD pathology

BIRTH

P10

1-24 hrs post-IR

3-15 M post-IR

Delayed effects

X-rays

0 Gy

0.5 Gy

1.8 Gy

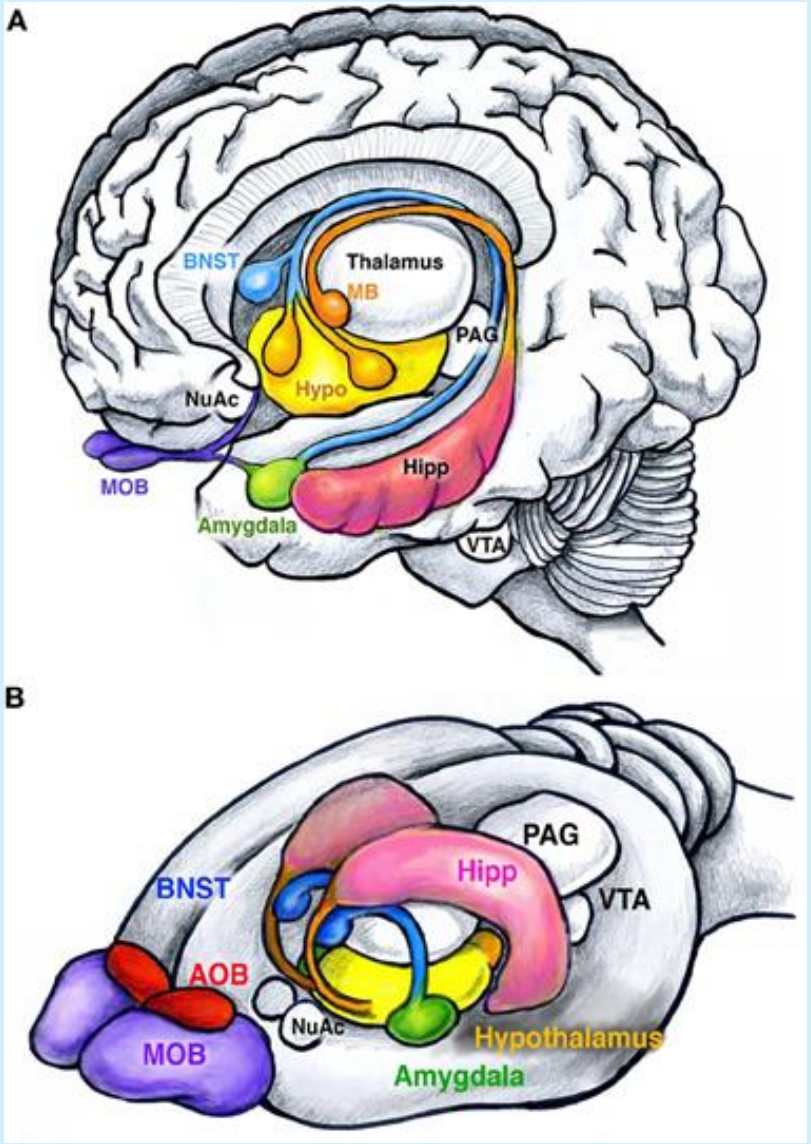
3xTg AD mice

Female

BIRTH

P

Focus on **hippocampus**



Sokolowski 2012 Frontiers in Molecular Neuroscience

& oxidative stress
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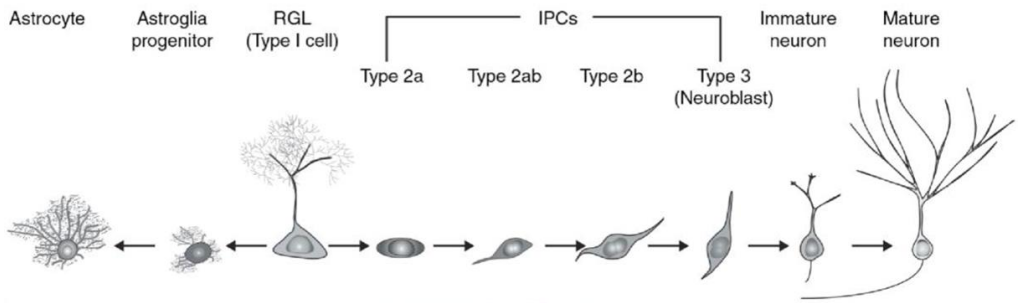
Plasticity
AD pathology

3-15 M post-IR

Delayed effects

Radiation & Alzheimer's – Is there a link?

Dentate Gyrus



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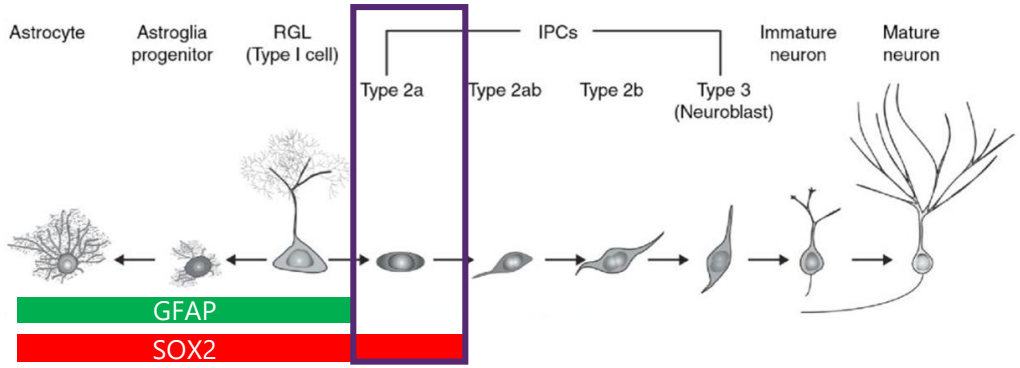

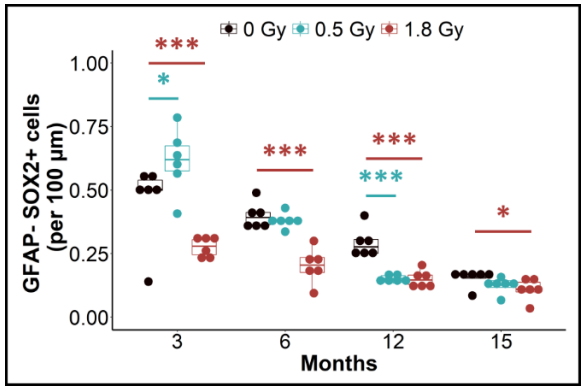

Radiation & Alzheimer's – Is there a link?

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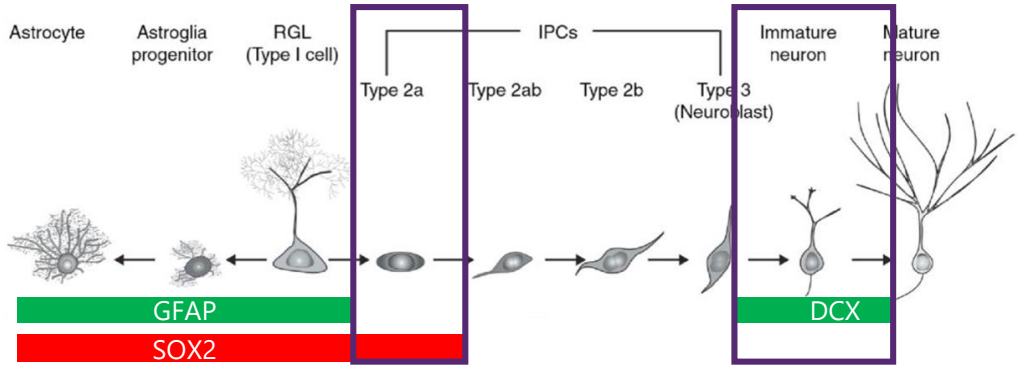

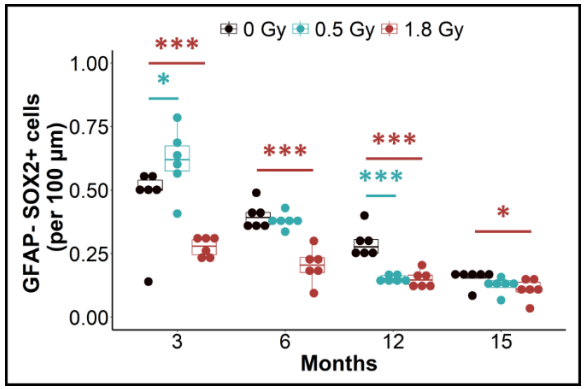

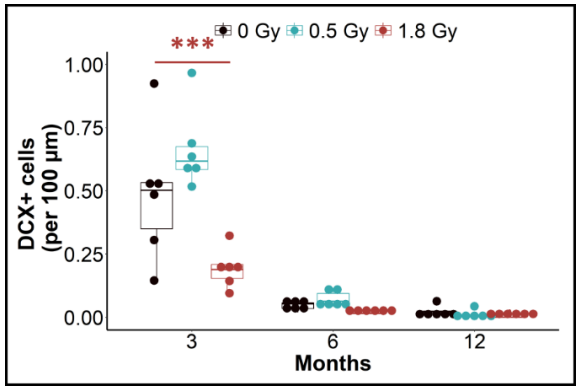

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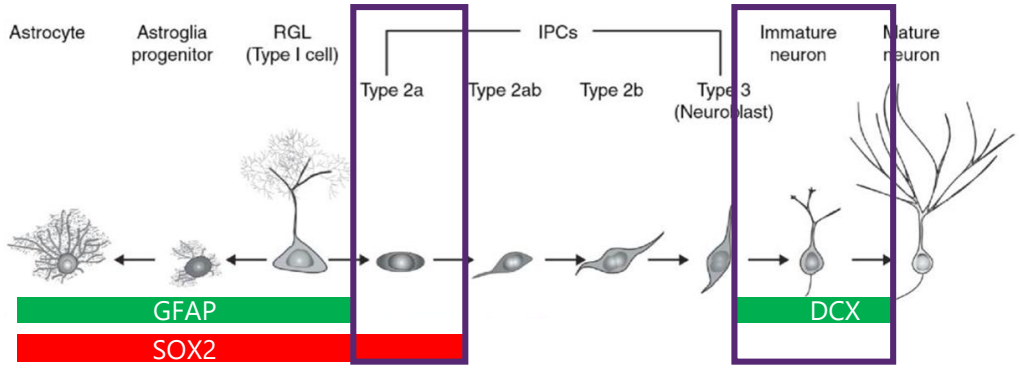

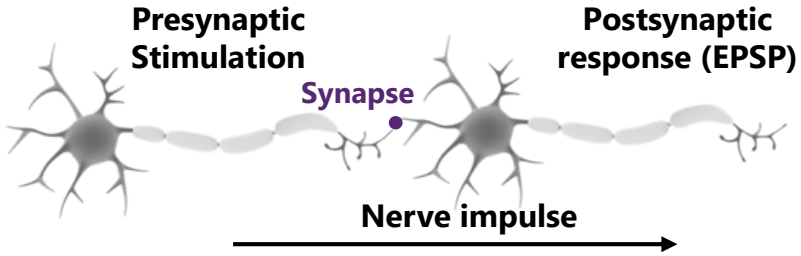

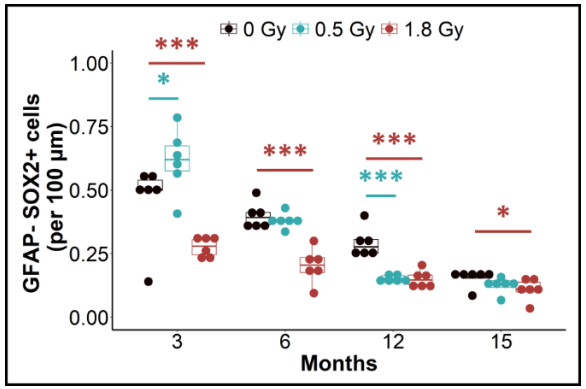

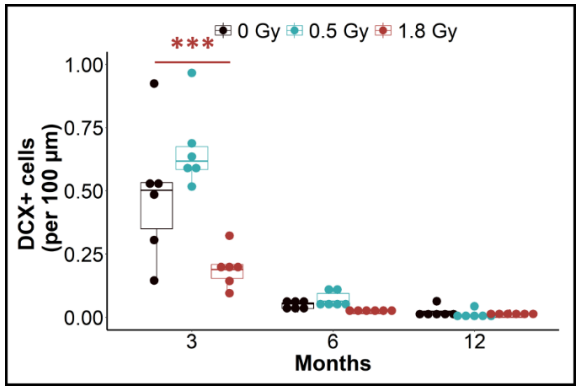

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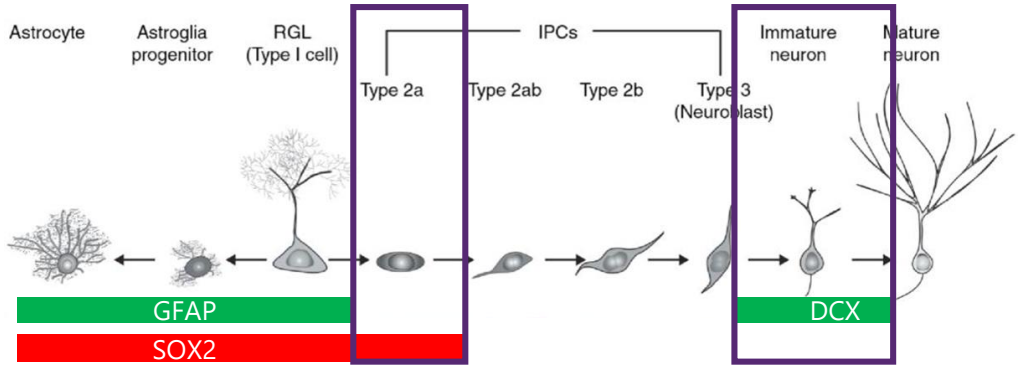
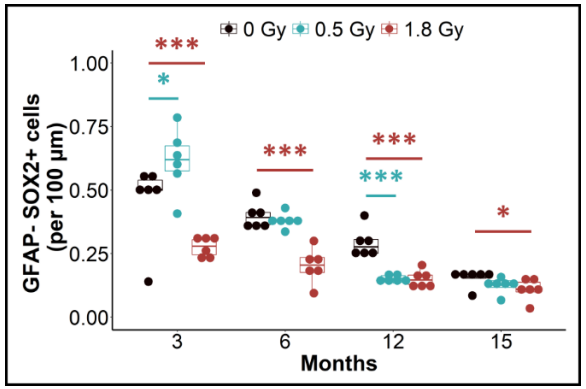
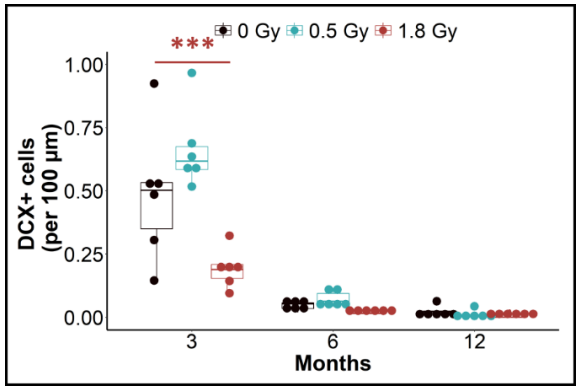
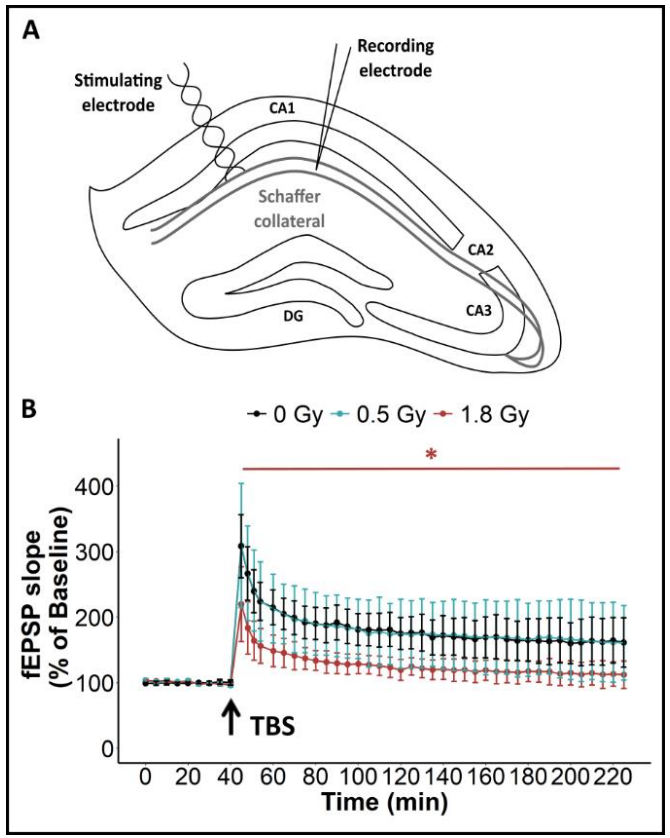


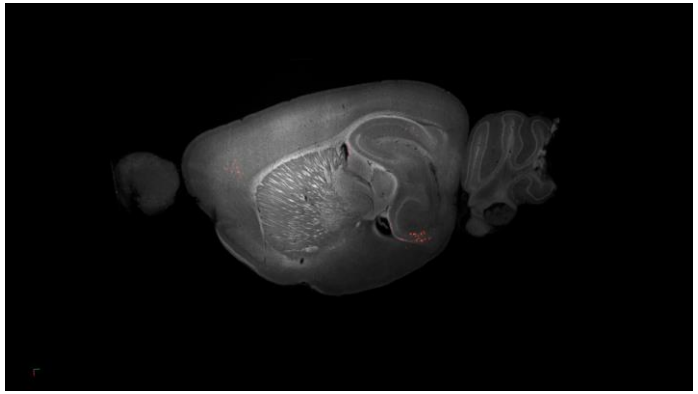


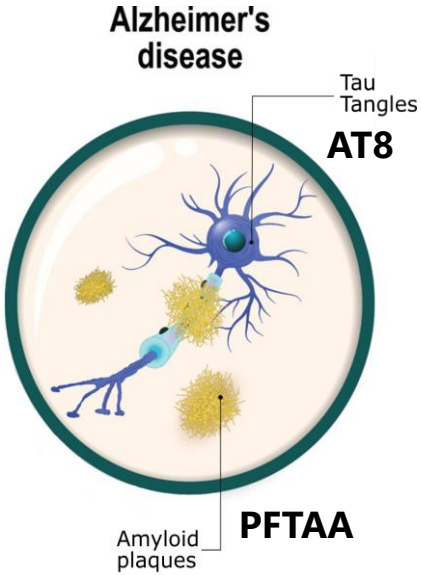




Radiation & Alzheimer's – Is there a link?

Tissue clearing

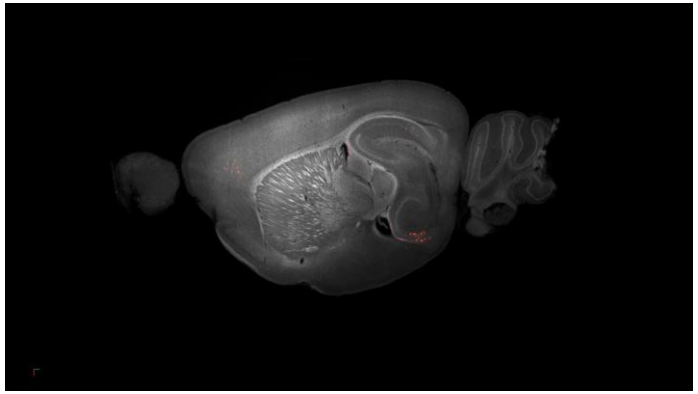


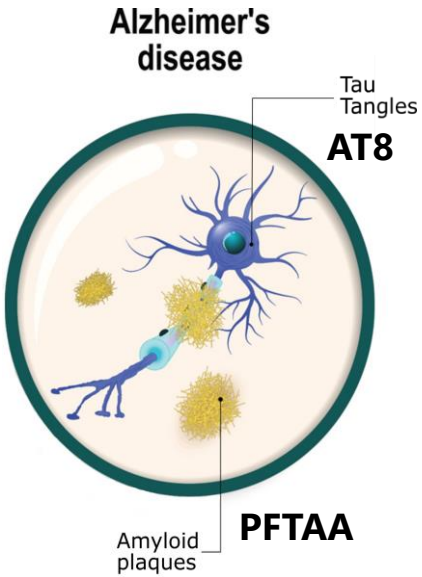


OHSU Brain Institute
2020

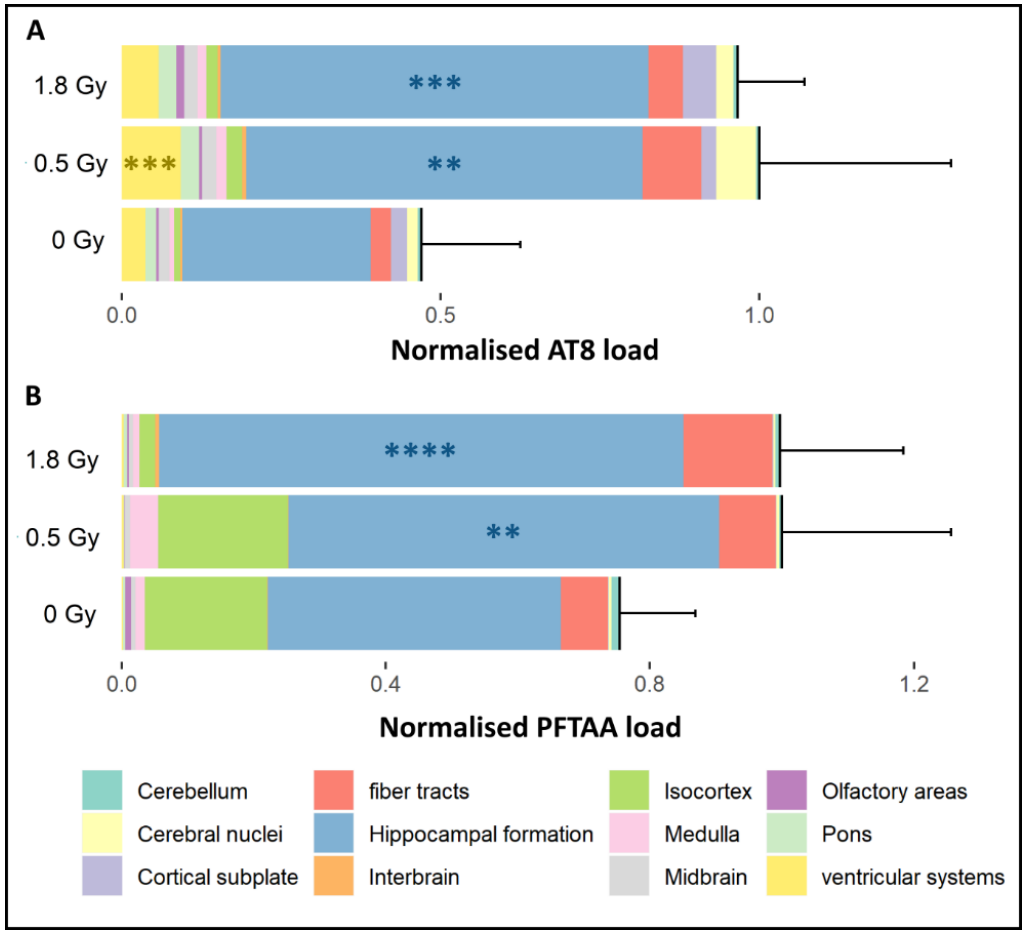
Radiation & Alzheimer's – Is there a link?

Tissue clearing



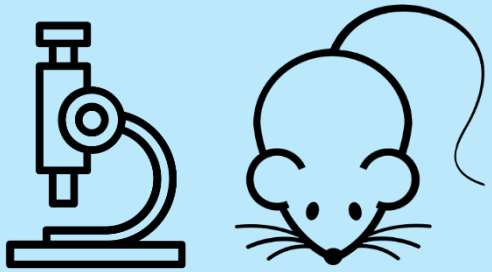


OHSU Brain Institute 2020



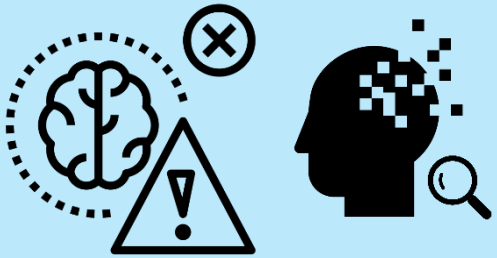
What is next?

Extending fundamental knowledge



Improving and extending follow-up

Screening for Alzheimer's predisposition



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