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Whole brain versus targeted dentate gyrus irradiation model to explain low to moderate doses of exposure effects in mice

Christelle Durand

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IRSN

INSTITUT
DE RADIOPROTECTION
ET DE SÛRETÉ NUCLÉAIRE

Faire avancer la sûreté nucléaire

Whole brain *versus* targeted dentate gyrus irradiation models to explain low to moderate doses of exposure effects in mice

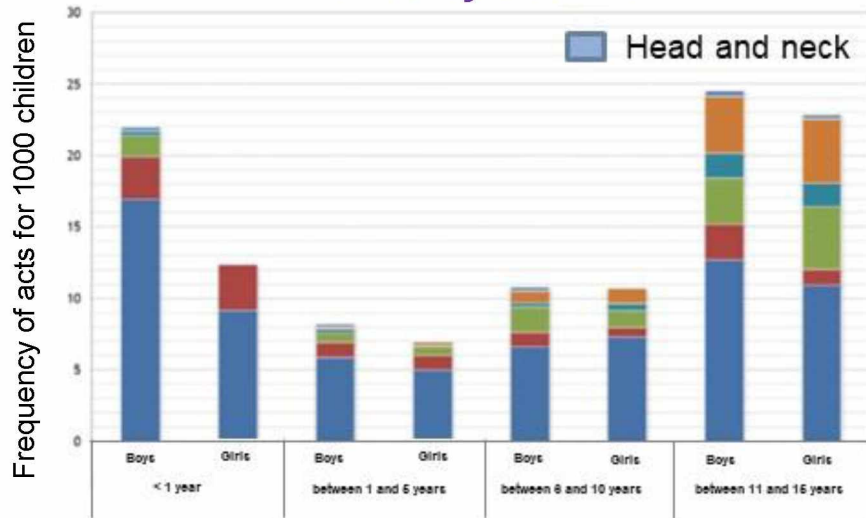
C. Durand Laboratory of Experimental Radiotoxicology and Radiobiology, IRSN

- **Children's brain can be exposed at low to moderate (< 2 Gy) doses of ionizing radiation (IR) during medical procedure**

➔ Children's brain can be exposed at low to moderate (< 2 Gy) doses of ionizing radiation (IR) during medical procedure

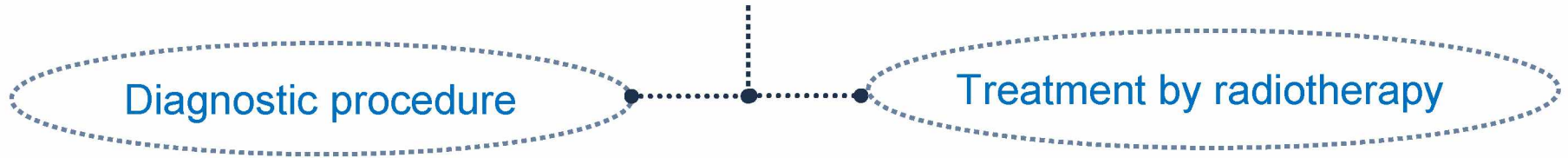
Diagnostic procedure

Head and neck are the most explored zones by scanner

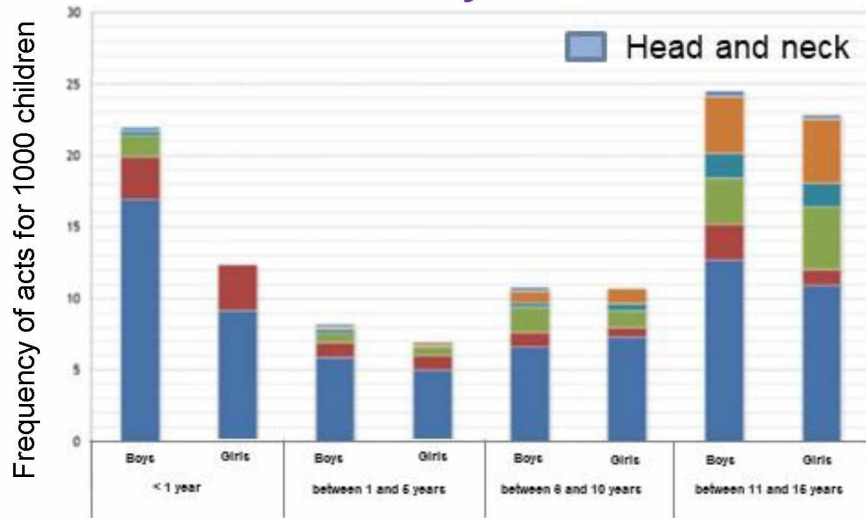


IRSN_NRD-Bilan 2013-2015-Diagnostic-Medical

➔ Children's brain can be exposed at low to moderate (< 2 Gy) doses of ionizing radiation (IR) during medical procedure

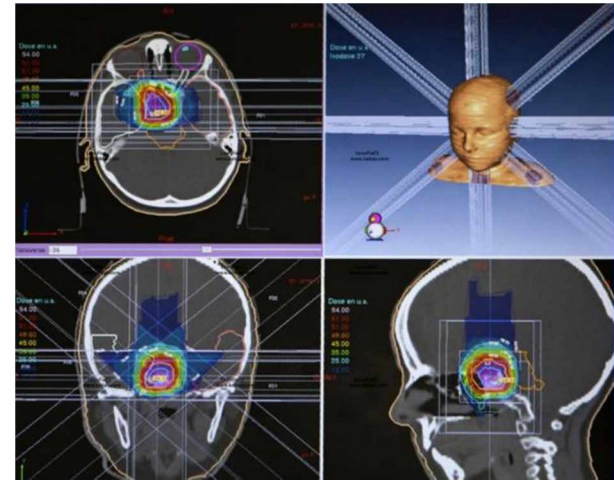


Head and neck are the most explored zones by scanner



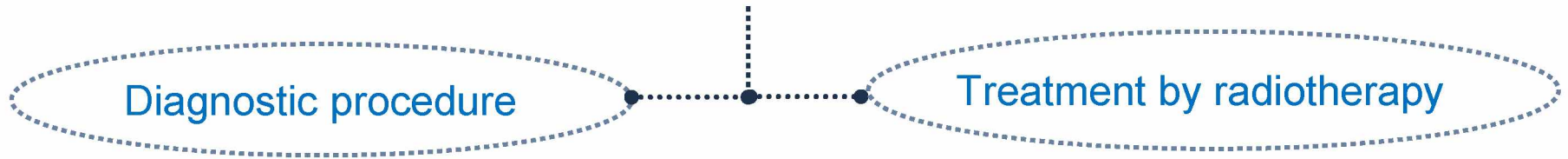
IRSN_NRD-Bilan 2013-2015-Diagnostic-Medical

Can be used to eradicate cerebral tumors



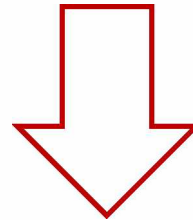
500 new cases of cerebral tumors detected (children under 18 years old) / year in France (Institut Curie 2017)

- Children's brain can be exposed at low to moderate (< 2 Gy) doses of ionizing radiation (IR) during medical procedure



Head and neck are the most explored zones by scanner

Can be used to eradicate cerebral tumors



Whole brain or some brain regions can be exposed.

- Lack of knowledge about the long-term consequences of children's brain exposure at low to moderate (< 2 Gy) doses of IR



Cognitive (Hall et al., 2004 ; Ron et al., 1982) and mood (Ron et al., 1982) disorders are suggested.

BUT

Few number of studies exist and their results can be controversial (Blomstrand et al., 2014) and difficult to interpret.

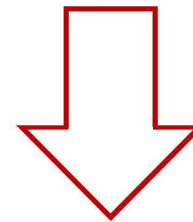
- Lack of knowledge about the long-term consequences of children's brain exposure at low to moderate (< 2 Gy) doses of IR



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BUT

Few number of studies exist and their results can be controversial (Blomstrand et al., 2014) and difficult to interpret.

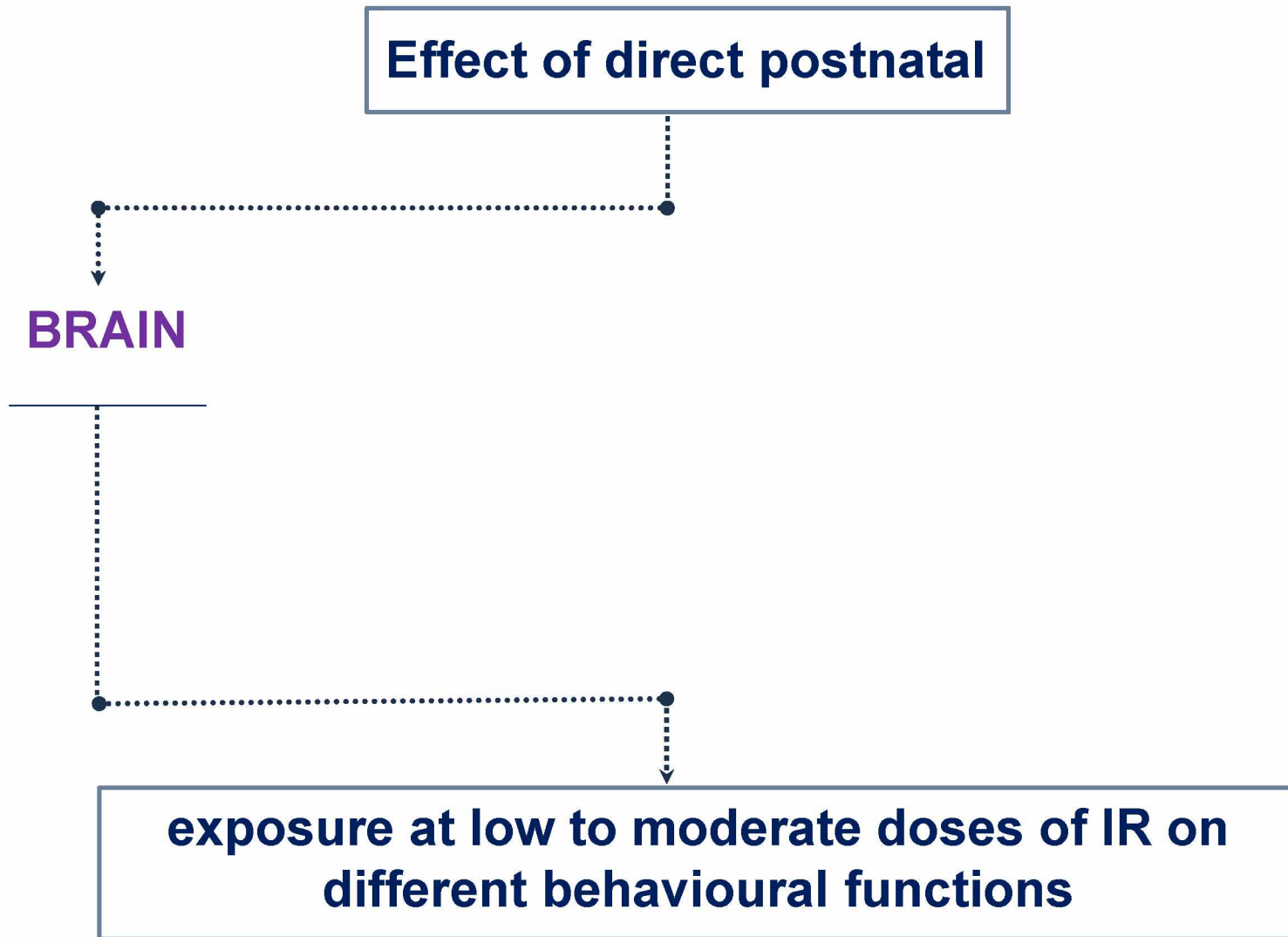


Experimental studies are necessary

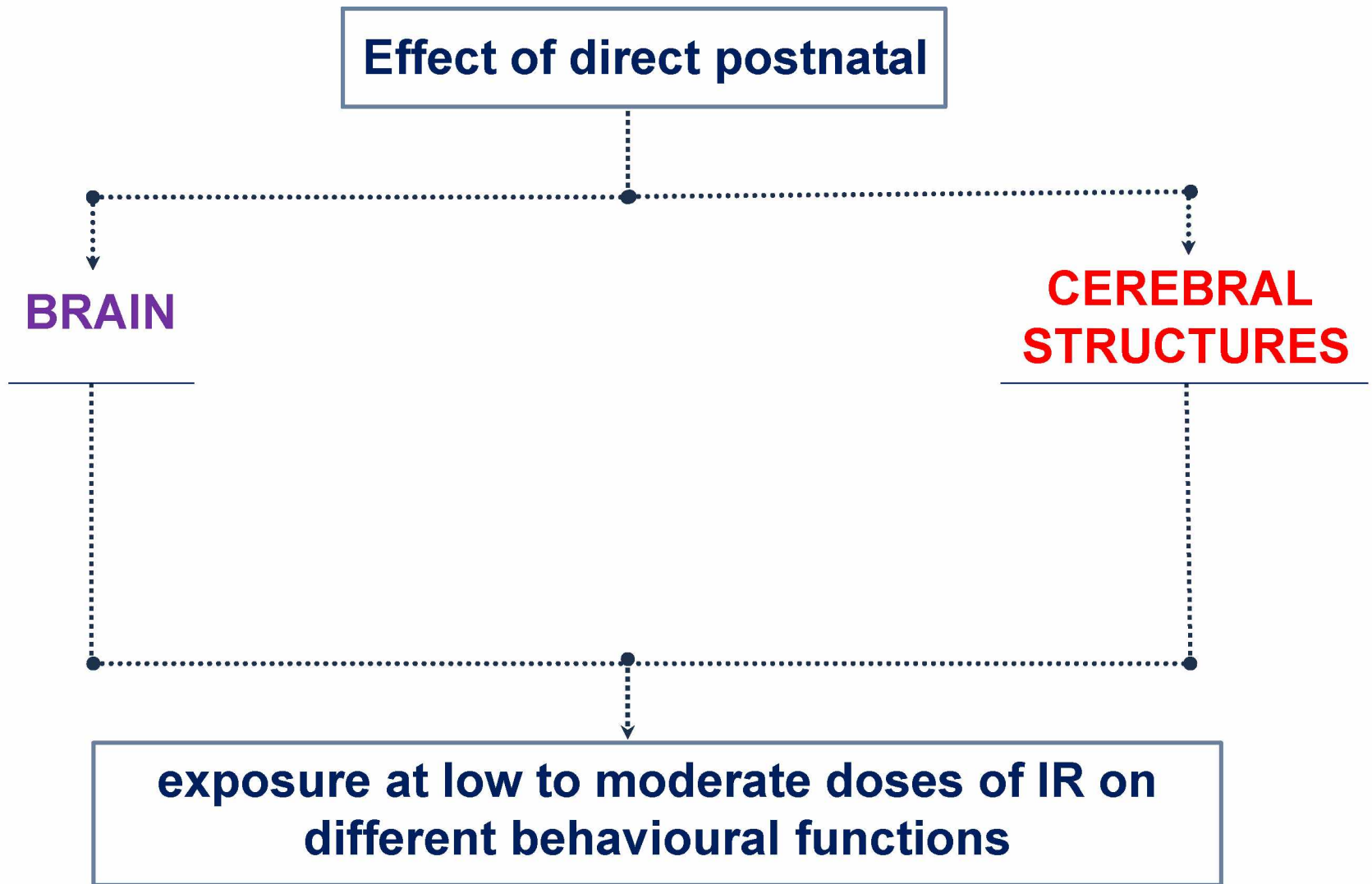
➤ Objectives

**exposure at low to moderate doses of IR on
different behavioural functions**

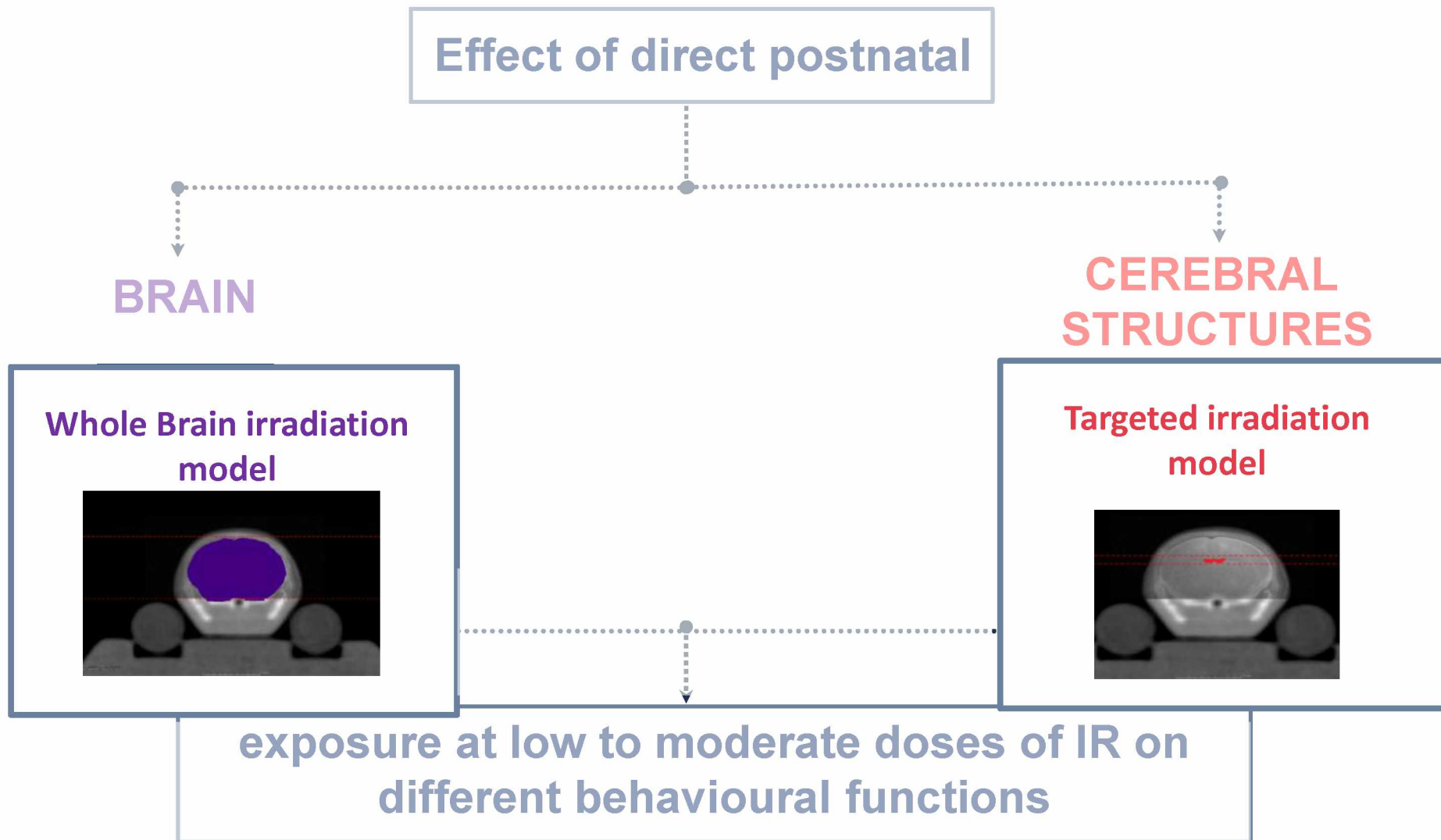
➤ Objectives



➤ Objectives



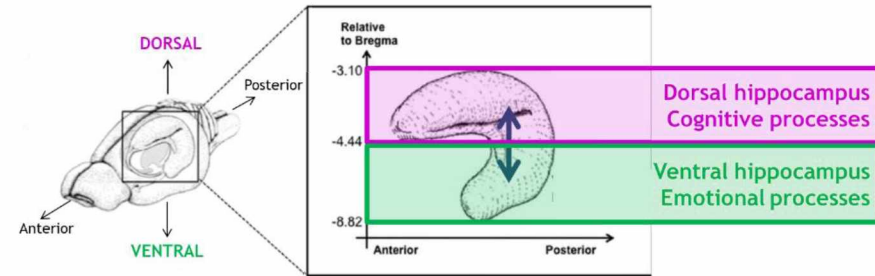
➤ Experimental strategy



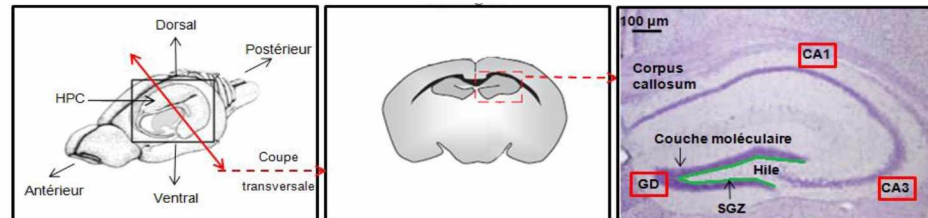
➤ Structure of interest : The dentate gyrus (DG) of the hippocampus

➔ Hippocampus

❖ Play a major role in cognitive (dorsal part) and emotional (ventral part) processes (Fanselow et al., 2011).



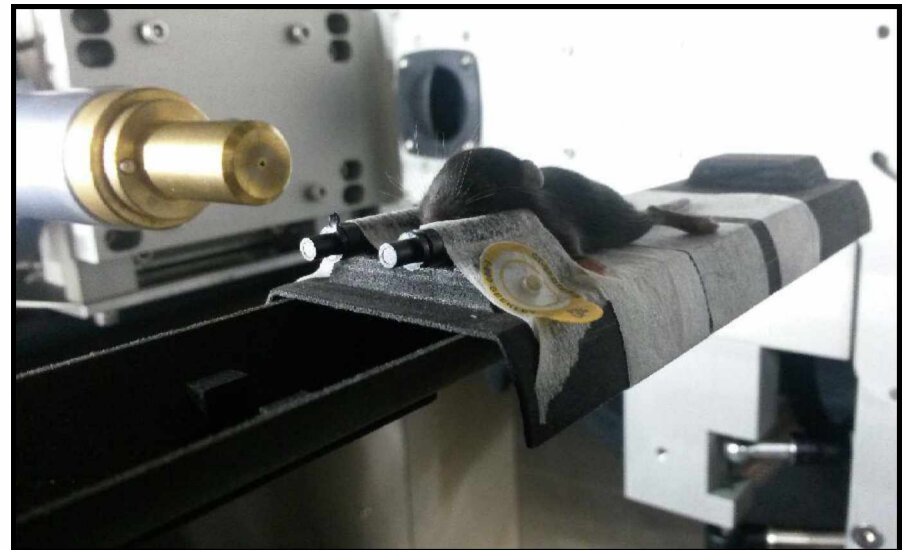
➔ In the subgranular zone of the **DG**, postnatal and adult neurogenesis, plays an important role in several “hippocampal-dependent” forms of memory (Castilla-Ortega et al., 2011) and in the enhancement of stress response (Snyder et al., 2011, Petrik et al., 2012).



➤ Model development in 10 days mice (Dos Santos et al., 2018):



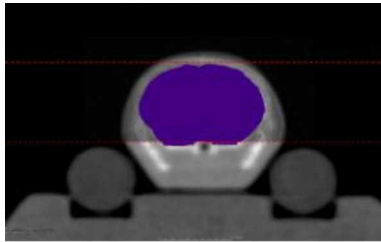
Small Animal Radiation Research Platform



Technical development to obtain a high ballistic specificity and to irradiate at low to moderate doses (Range doses : 0.25 – 2 Gy).

➤ Model development in 10 days mice (Dos Santos et al., 2018):

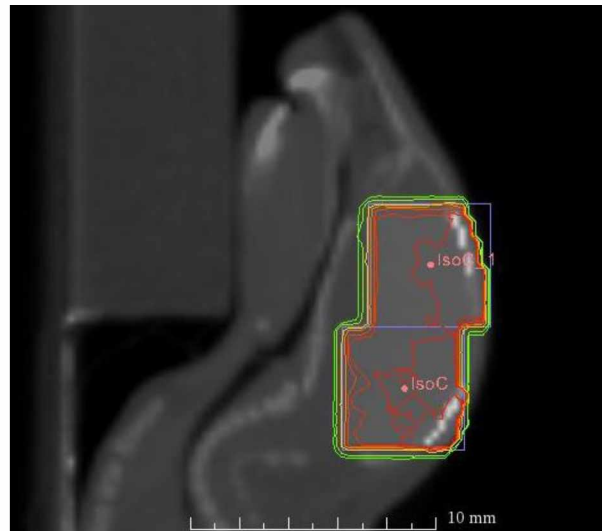
Whole Brain irradiation model



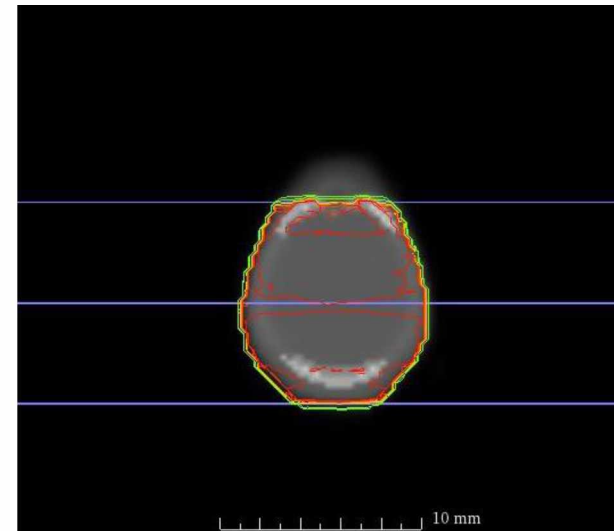
- Only CBCT images on the SARRP
- Irradiation field: $5 \times 5 \text{ mm}^2$
- 2 isocenters
- 2 beams at 180° per isocenter perpendicular to the sagittal plan



Transversal



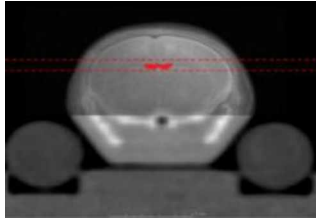
Sagittal



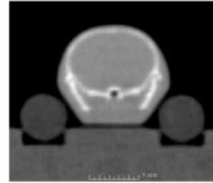
Coronal

➤ Model development in 10 days mice (Dos Santos et al., 2018):

Targeted irradiation model

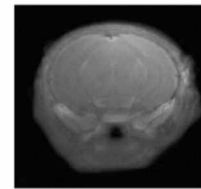
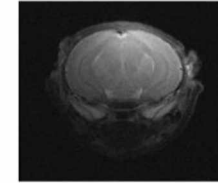


Acquisition of CBCT images on the SARRP



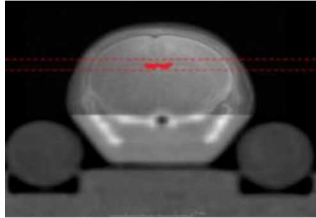
+

Acquisition of 2D MRI images (Bruker, 4.7 Teslas)



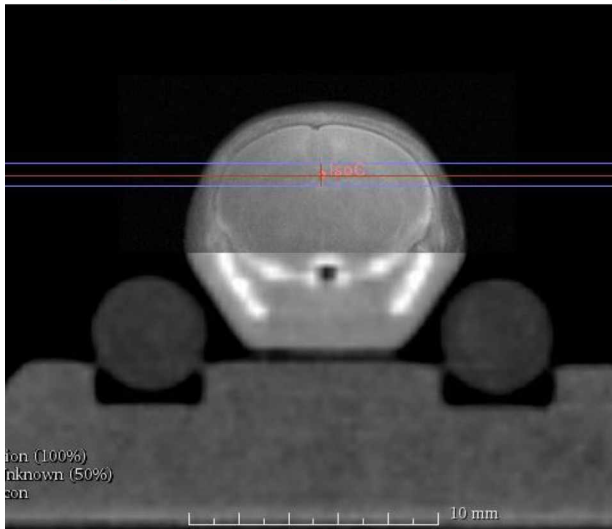
➤ Model development in 10 days mice (Dos Santos et al., 2018):

Targeted irradiation model

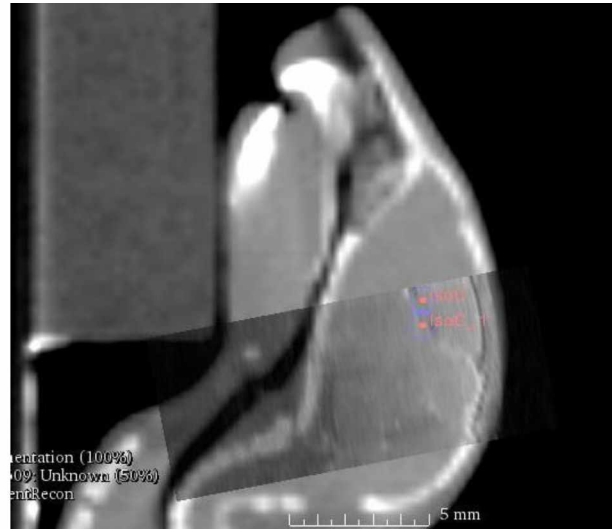


- Superposition of MRI and CBCT images
- Irradiation field: 1 mm
- 2 isocenters
- 2 beams at 180° per isocenter perpendicular to the sagittal plan

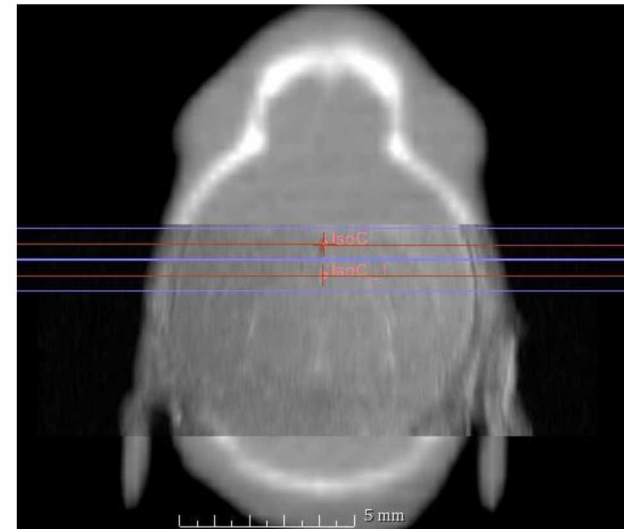
Dorsal Dentate Gyrus (DG_D) targeted model of irradiation



Transversal



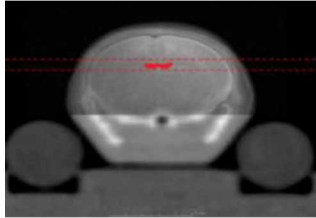
Sagittal



Coronal

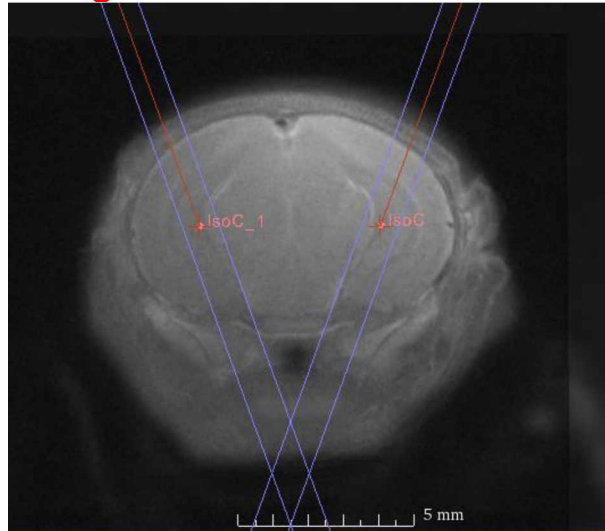
➤ Model development in 10 days mice (Dos Santos et al., 2018):

Targeted irradiation model

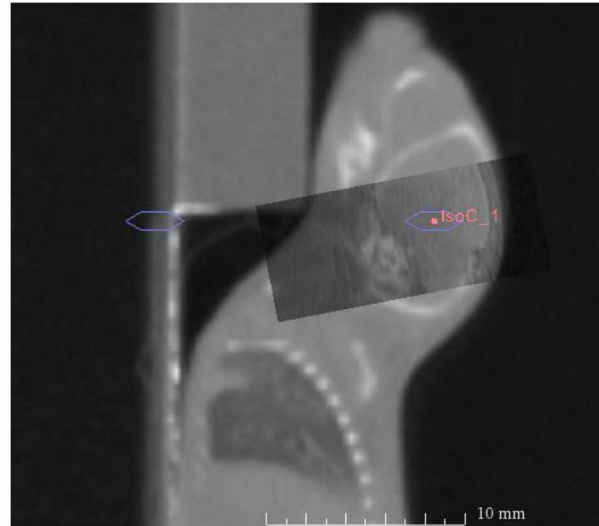


- Superposition of MRI and CBCT images
- Irradiation field: 1 mm
- 2 isocenters
- 1 beam per isocenter

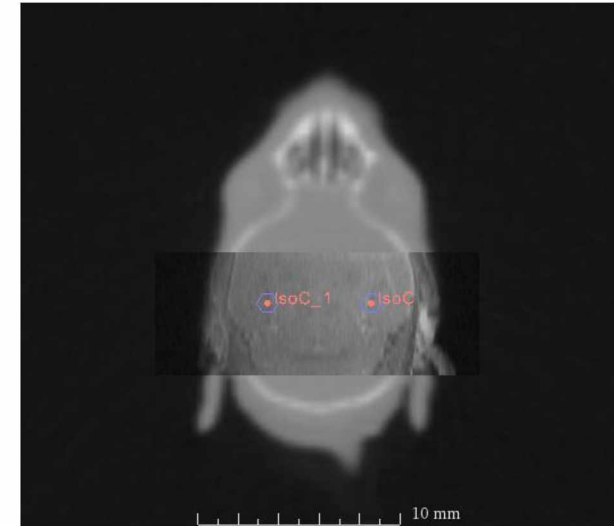
Ventral Dentate Gyrus (DG_V) targeted model of irradiation



Transversal



Sagittal



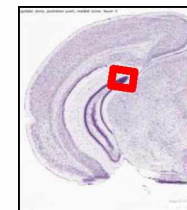
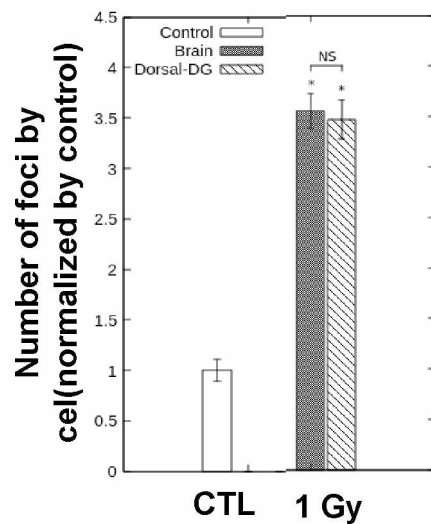
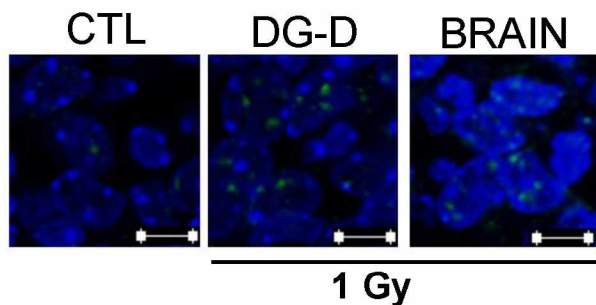
Coronal

➔ Model development in 10 days mice (Dos Santos et al., 2018):

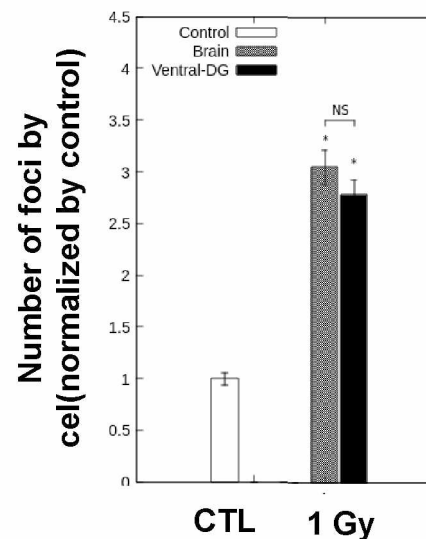
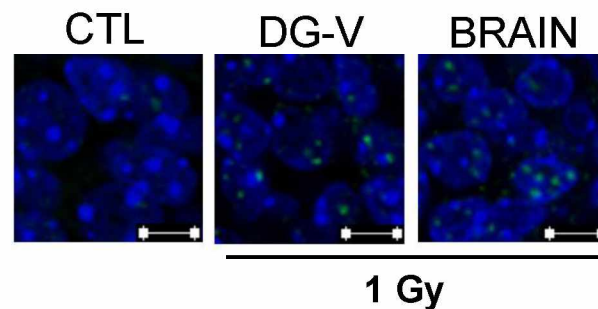
Ballistic validation using γ -H2AX staining (γ -H2AX / DAPI)



Dorsal DG targeted model



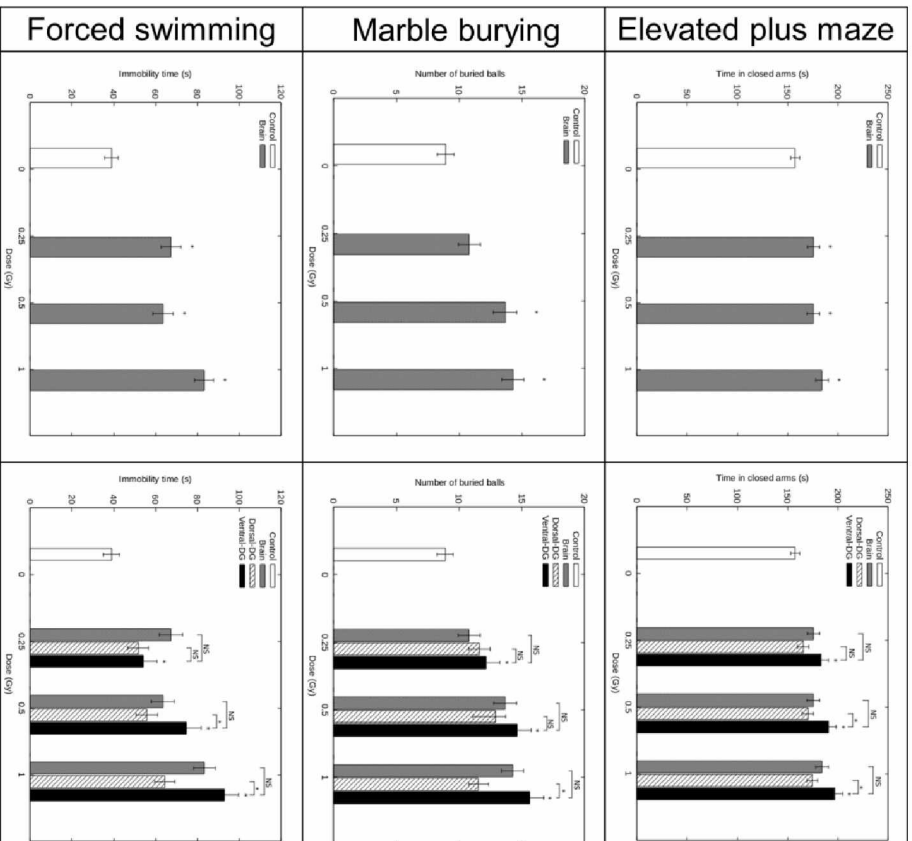
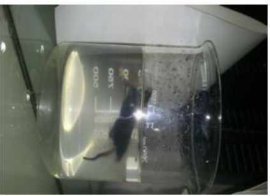
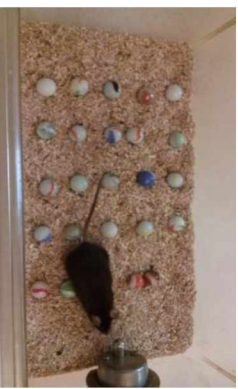
Ventral DG targeted model



*: p-value < 0,05 vs control

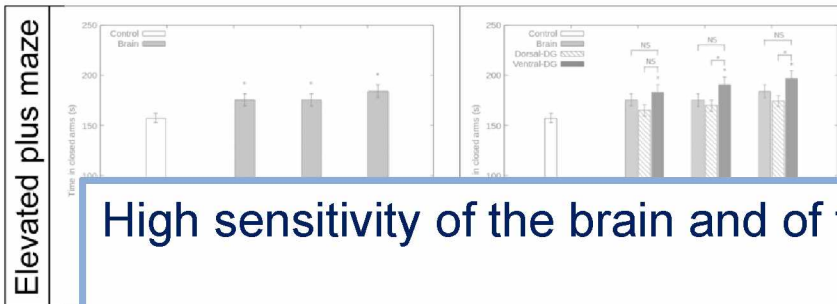
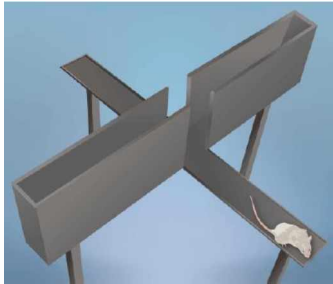
➔ Results (3 months after exposure)

✓ Anxiety / depressive like behaviours (Dos Santos et al., 2018)



➤ Results (3 months after exposure)

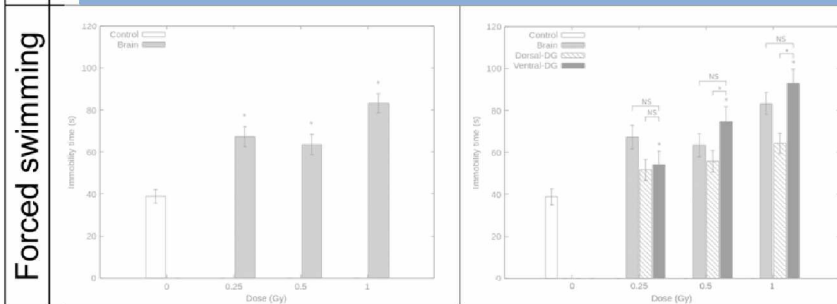
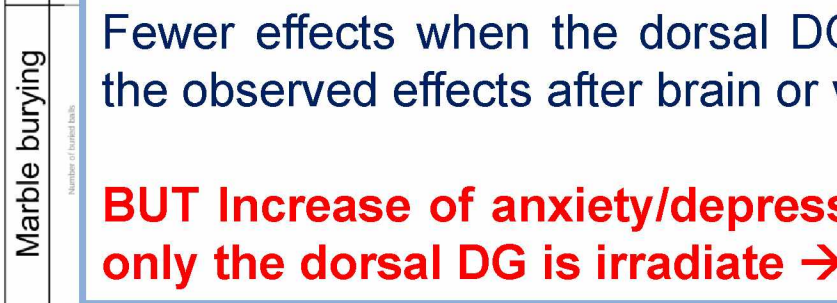
- ✓ Anxiety / depressive like behaviours (Dos Santos et al., 2018)



High sensitivity of the brain and of the ventral DG.

Fewer effects when the dorsal DG is exposed (compared to the observed effects after brain or ventral DG exposure).

BUT Increase of anxiety/depressive like behaviours when only the dorsal DG is irradiate → indirect effect of IR



➤ Results (3 months after exposure)

Spatial learning and memory after 1 Gy exposure of whole brain or of the dorsal DG

Results of the retention probe:

	Paradigm	Open filed			Water Maze
	Memory	Short term		middle term	Long term
	Learning task	simple	Neurogenesis dependant	complex	neurogenesis dependant
Group vs CTL	BRAIN 1 Gy	×	×	* <0,05	×
	DG-D 1 Gy	×	×	×	* < 0, 05

Unpublished data

* p<0,05 One way anova.
 × means « no significant difference with the control group.

C. Serrano, phd student
 M. Ben Sidhoum

- Using SARRP facility, we developed new models that allow to elucidate direct IR (<2 Gy) effects of postnatal brain or cerebral structures exposure, in mouse.
- High sensitivity of the developing brain or some cerebral regions to IR regarding the development of anxiety/depressive like behaviours in mouse.
- Indirect effects of IR → « bystander effect » observed using those models
- Cognitive disturbance seems to depend on the dose, the irradiated volume, the type of memory, the learning task.

 **IMPORTANT FOR CHILDREN RADIOPROTECTION SYSTEM**

Thank you for your attention!

Thank you for your attention!

M. Dos Santos
P. Lestaevel
C. Serrano
M. Ben Sidhoum
D. Kereselidze
C. Gloaguen
R. Poirier

