Effects of ionizing radiation on learning and spatial memory after postnatal mouse brain exposure at low to moderate doses

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Introduction

For **Computed tomography scan**, the exploration of the head and neck are dominant in pediatrics . **Long-term effects** of brain exposure, at **low to moderate doses** (≤ 2 Gy) of ionizing radiation on cognitive functions, such as **learning and memory processes**, are not well established in humans and are an important scientific issue. Among brain structures, the **hippocampus** has a major role in memory processes. In the subgranular zone of the dentate gyrus of the hippocampus, **new neurons** are continuously generated during postnatal and adult life and play an important role in several "hippocampal-dependent" forms of memory (Zhao et al., 2008 ; Gonçalves et al., 2016). The effects of brain irradiations at low to moderate doses on those processes are not clearly established.

Objectives

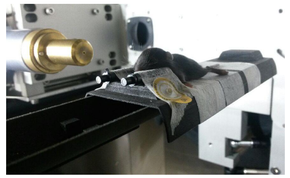
The aims of our project are to study the impact of postnatal irradiation at low to moderate doses in a mouse model:

1) on spatial learning and memory using a water maze task
2) on adult hippocampal neurogenesis, and
3) to compare two models of irradiation exposure: **whole brain** *vs* **dorsal dentate gyrus**

Irradiation procedure : two models of exposure

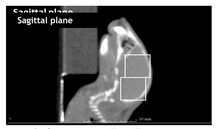
M. Dos Santos et al., 2018

The irradiations were performed on the SARRP (Small Animal Radiation Research Platform). Thanks to the onboard imaging system, the treatment planning system and the superposition with MRI images, it is possible to irradiate the **whole brain** or more specially our structure of interest : **the dorsal dentate gyrus**.



10 days old mice were anesthesied and disposed into the SARRP. Mice of the control group underwent scanner imaging as irradiated mice.

Brain irradiation model



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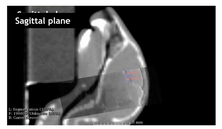
Dorsal Dentate Gyrus irradiation model



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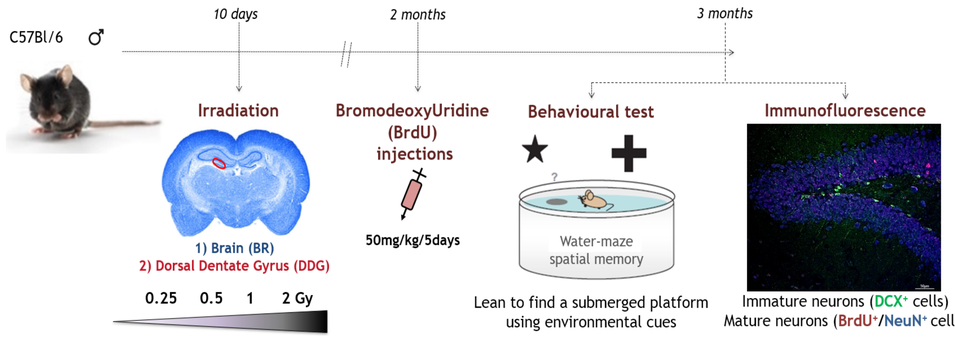
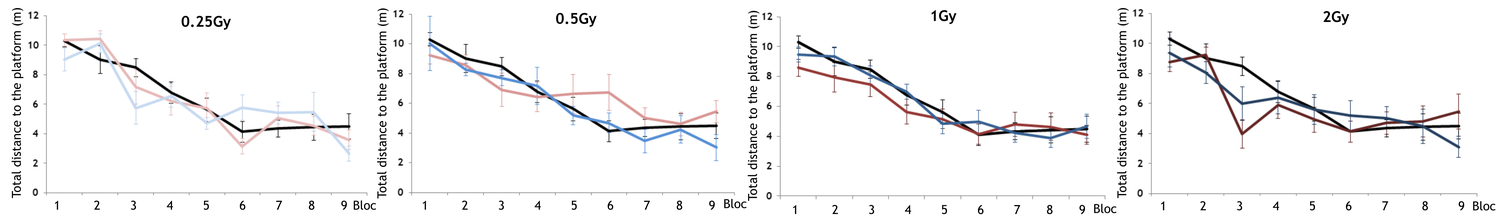
For each procedure, two isocenters are positioned. The direction of the treatment plane is perpendicular to the sagittal plane. In order to have a homogeneous distribution of the dose for each isocenter, two beams at 180° are delivered.

Experimental strategy



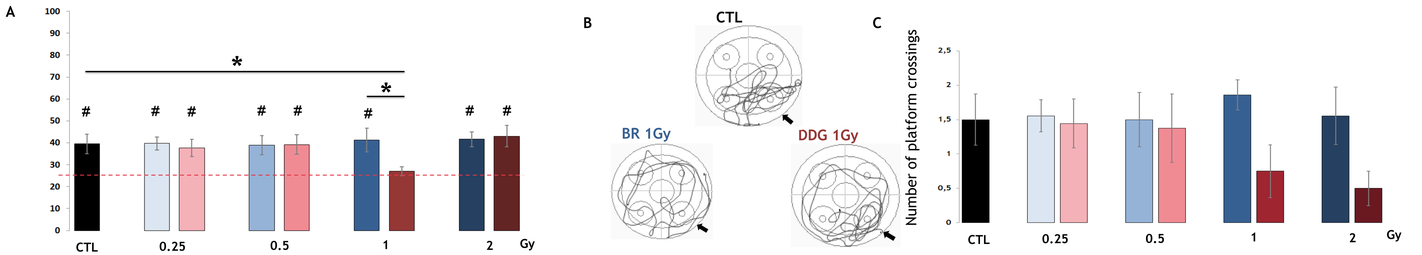
Results : spatial learning and memory in water maze task

In both models ionizing radiation not induce spatial learning impairments, whatever the dose



Distance swum to reach the platform *(mean ± SEM ; **CTL** (n = 15), **BR** (n = 8 to 11), **DDG** exposure (n = 7 to 11)*. All mice from each model of exposure learned the location of the platform *(Anova with repeated measures, p<0,05)*.

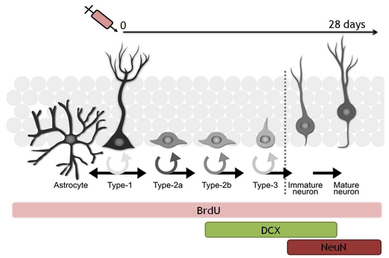
Overall brain exposure does not induce mnesic impairment at all dose
Targeted exposure of DDG induces mnesic impairment only at a dose of 1Gy

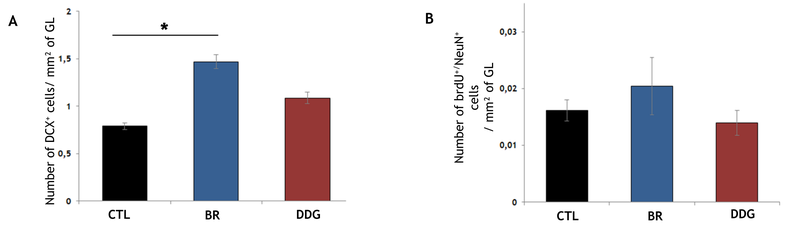


(A) Percentage of distance in the correct quadrant *(mean ± SEM ; **CTL** (n = 15), **BR** (n = 8 to 11), **DDG** exposure (n = 7 to 11)*. Mnesic impairment appears at a dose of 1Gy *(One simple t-test (25% : materialized by red line), # p<0.05 ; One way Anova, *p<0,05)* but not at a greater dose of 2Gy after targeted exposure of the DDG. This impairment is not found after all brain irradiation for each dose. (B) Representative trial profiles of CTL, BR and GDD exposed at 1Gy *(white arrow : starting platform ; black arrow : platform quadrant)*. (C) Number of crossings *(mean ± SEM ; **CTL** (n = 15), **BR** (n = 8 to 11), **DDG** exposure (n = 7 to 11)*.

Preliminary results : Adult hippocampal neurogenesis study after irradiation at 1Gy

All brain exposure at the dose of 1Gy increased immature neurons density in the DDG





(A) Density of immature neurons (DCX+ cells) on the granular layer (GL) *(mean ± SEM, n = 5 to 6)*. (B) Density of mature neurons (BrdU + /NeuN + cells) on the GL *(mean ± SEM , n = 3 to 5)*. To understand the differents effects observed between global or targeted exposure of the DDG, we have chosen to study the impact of IR at the dose of 1Gy on the process of neurogenesis. Our preliminary results have showned that densities of immature neurons (DCX+ cells) are significantly different between groups *(Kruskal-Wallis, p = 0,047; Dunn's methods, * p<0,05)*. There are no effect on 28 days old neurons.

Conclusions / Perspectives

Our results demonstrate that dose response relationships is not linear, in the context of a targeted exposure. In the two models, the DDG received a dose of 1Gy. The comparison between the two models allowed us to emphasize that spatial memory impairments appared only after targeted exposure of the DDG at this dose. To understand this imparment at 1Gy, the density of immature and mature neurons is being completed, and the density of proliferative cells will be studied. The inflammatory response in the two models at the dose of 1Gy, will help us to understand the mnesic impairments observed. Finally, other behavioural tasks are being performed to study if other cognitive functions are altered by ionizing radiation in the two models at the dose of 1Gy.

Zhao, C., Deng, W., & Gage, F. H. (2008). Mechanisms and functional implications of adult neurogenesis. Cell, 132(4), 645-660. Gonçalves, J. T., Schafer, S. T., & Gage, F. H. (2016). Adult neurogenesis in the hippocampus: from stem cells to behavior. Cell, 167(4), 897-914. M. Dos Santos, D. Kereselidze, C. Gloaguen, M.A. Benadjaoud, X. Tack, P. Lestaevel and C. Durand (2018) Development of whole brain versus targeted dentate gyrus irradiation model to explain low to moderate doses of exposure effects in mice. 2018 Nov 22;8(1):17262.
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