

# The Dose Response of the Developing Mouse Brain after Cranial Irradiation Varies by Brain Structure

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## Target Audience

This work is of interest to those involved in the planning of or follow-up after cranial radiation therapy for paediatric cancer treatment or in the study of late-appearing cognitive side effects. It is also of interest to those studying brain development using the mouse as a model system.

## Introduction

Cranial irradiation is part of the standard of care for paediatric patients with acute leukaemia and brain tumours. While radiation therapy confers a long-term survival benefit, it has also been implicated in the development of neurocognitive late effects, most often measured as a progressive decrease in IQ<sup>1</sup>. In the human patient population, younger age at the time of irradiation, female sex, the dose delivered, and the volume irradiated are considered risk factors for the development of late effects<sup>2</sup>. We have previously shown that radiation-induced alterations in brain development can be measured using longitudinal MRI<sup>3</sup>. The goal of the current work is to characterize how radiation-induced alterations in mouse brain development depend on delivered dose and subject sex.

## Methods

Anaesthetized C57Bl/6J pups (n=5-7 each of males and females per dose group) received whole-brain irradiation to doses of 3, 5, or 7 Gy from a <sup>137</sup>Cs source at 2.5 weeks of age. The rest of the body was shielded by 3.2 cm of lead, restricting doses there to ~0.4 Gy. Control mice were also anaesthetized, but were not irradiated. *In vivo* MRI was performed at 7 T using a 3D gradient echo sequence (125  $\mu$ m isotropic resolution, TR/TE/ $\alpha$ =100 ms/4 ms/55°) prior to irradiation at 2 weeks of age, and then following irradiation at 3.5, 6, 9, and 14 weeks of age. At all imaging time points, mice were administered 0.4 mmol/kg MnCl<sub>2</sub> intraperitoneally 24 hrs prior to imaging.

The images from all time points were registered together to generate an unbiased average image space. Using a segmented atlas with 62 labelled brain structures, the Jacobian determinants from the deformation fields were used to compute absolute brain structure volumes for each image. Statistical analysis of the data was performed using a non-linear mixed effects model, which fit an exponential growth curve to the data, allowing an offset for the pre-irradiation time point and including random offsets to account for variability among individual mice. The asymptotic volume was allowed to vary with radiation dose and sex, as well as the interaction between them, and the term corresponding to the volume at 3.5 weeks was allowed to vary with dose. All of the other terms in the fit were common to all doses and sexes. Multiple comparisons were controlled for using the false discovery rate (FDR).

## Results

Figure 1 is a map indicating structures for which the asymptotic volume decreases significantly as the radiation dose is increased (10% FDR). The map indicates the long-term volume deficit of the structures in mice irradiated with 7 Gy relative to unirradiated mice (larger differences are indicated by hot colours). The olfactory bulbs have the largest volume deficit, with a 14% smaller volume after 7 Gy compared to controls.

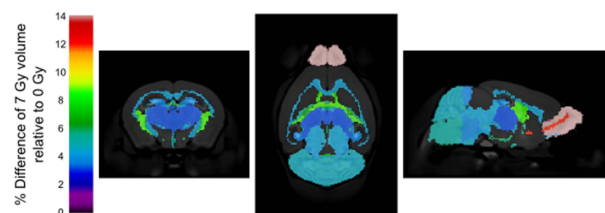
Figure 2 shows the volume of the olfactory bulbs over time along with the model fits. The volume of this structure is significantly smaller with increasing dose, both early after irradiation (10% FDR) and long-term (1% FDR).

Figure 3 shows the total white matter volume over time. Overall, the white matter is affected by the radiation more strongly than the gray matter, as indicated by a significant dose effect both early post-irradiation (p<0.05) and long-term (p<0.01). The total gray matter shows a trend towards a long-term dose effect (p=0.07), but a weaker early effect.

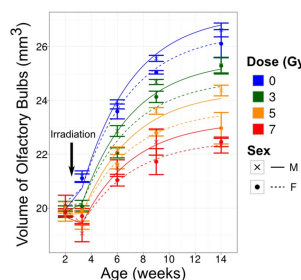
## Discussion and Conclusion

Cranial irradiation has been implicated in the development of neurocognitive late effects in childhood cancer survivors, but the underlying mechanisms and the roles of various risk factors remain poorly understood. Using longitudinal *in vivo* MRI, this study shows that the dose response following irradiation at a young age varies with structure in the developing mouse brain. While some structures appear to be minimally-affected by the radiation, others show a lasting volume deficit that increases with dose. Knowledge of the dose sensitivity of different brain structures may help balance the need for local tumour control and the risk for detrimental side effects during treatment planning. We are investigating the importance of specific cell populations in different structures with the aim of understanding the underlying cellular mechanisms. While it has been observed that females are more susceptible to late effects following cranial irradiation than males in the human population, our data thus far have not indicated that this is the case for neuroanatomical changes in the mouse irradiated at 2.5 weeks of age.

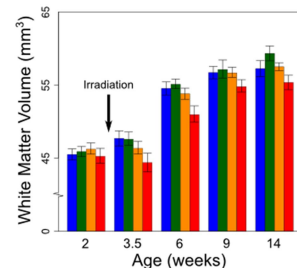
**References:** <sup>1</sup>Hoffman & Yock, J Child Neurol (2009) <sup>2</sup>Mulhern & Palmer, Curr Probl Cancer (2003) <sup>3</sup>Gazdzinski et al., Int J Radiat Oncol Biol Phys (2012)



**Fig 1.** Map indicating the long-term volume deficit of structures irradiated with 7 Gy relative to controls. All coloured structures have a significant dose effect for the asymptote term (10% FDR).



**Fig 2.** Volume of olfactory bulbs over time



**Fig 3.** Total white matter volume over time.