# Longitudinal Effects of Irradiation and Voluntary Exercise on Hippocampal Gray Matter Loss

Sarah Biedermann[1], Johannes Fuss[2], Claudia Falfán-Melgoza[3], Lei Zheng[3], Alexander Sartorius[3], Gabi Ende[1], Peter Gass[2], and Wolfgang Weber-Fahr[3]
[1]*Neuroimaging, Central Institute of Mental Health, Mannheim, Germany,* [2]*Animal Models in Psychiatry, Central Institute of Mental Health, Mannheim, Germany,* [3]*Translational Imaging, Central Institute of Mental Health, Mannheim, Germany*

**Introduction**

From studies in humans and rodents it is known that voluntary exercise is related to an increase of hippocampal gray matter assessed with MRI techniques [1, 2]. It is however not clear whether these findings result from the known hippocampal plasticity in the dentate gyrus through voluntary exercise [3, 4]. In an attempt to approach the underlying mechanisms of exercise induced gray matter increase, we performed hippocampal irradiation - which effectively inhibits hippocampal neurogenesis [5] - in one half of afterwards voluntary wheel-running mice. Structural profiles of the whole brain before and after the exercise period were assessed using in vivo Voxel-Based Morphometry (VBM) on a 9.4T animal scanner equipped with a cryogenic mouse-brain coil before and after the exercise period.

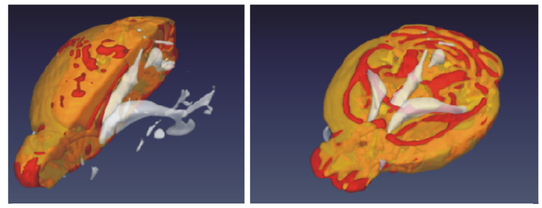

**Fig. 1:** Dartel group apriori template for gray matter (yellow), white matter (red) and cerebrospinal fluid (white).

**Methods**

45 C57BL/6N male mice were assigned to one of the treatment groups: hippocampal irradiation (IR) with 10 Gray in total or sham irradiation (SR) applied during a ketamine anesthesia. All mice were single-housed in Macrolon Type III cages, on a 12-h light-dark cycle. At the age of 9 weeks, 10 IR (IR-runner = IRR) and 10 SR (SR-runner = SRR) mice were given free access to a running wheel (diameter 11.5 cm), 10 IR (IR-sedentary = IRS) and 10 SR (SR-sedentary = SRS) had access to a blocked running wheel. After 6 to 8 weeks of voluntary wheel running (~9-10 km/night) all mice were investigated with structural MRI. Five animals of each group were additionally scanned before the period of exercise.

$T_2$-weighted high resolution 3D-morphometric data were acquired using a RARE-Sequence with a resolution of 78x78x156 µm at TE = 50 ms. The tissue segmentation of the MR images into gray matter (GM), white matter and CSF was performed in several steps, including brain extraction and group-specific a priori template creation with DARTEL using a 2-step subsequential individual segmentation with SPM8 described elsewhere [2] (Fig. 1). The segmented and normalized-modified tissue class images were smoothed with 0.4 mm Gaussian kernel and analyzed voxelwise with second level models over the whole brain (cross-sectional: two-sample t-tests; longitudinal: full factorial model with repeated measurements) [6].

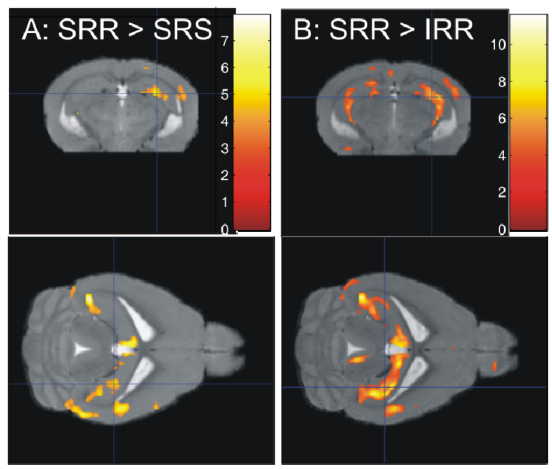


**Fig. 2:** Cross-sectional gray matter differences between non-radiated runners (SRR) and sedentary (SRS) (A) and SRR and radiated runners (IRR) (B) after exercise ($p < 0.001$ uncor.)

**Results**

Cross-sectional comparison of the VBM whole brain results after the treatment period revealed a significant cluster ($p<0.001$ uncorrected, min. 10 voxels) of increased hippocampal gray matter (GM) in SRR compared to SRS (Fig. 2A). Hippocampal GM was as well higher in SRR compared to IRR (Fig. 2B). In SRS the GM volume was higher compared to IRS. No significant differences were seen comparing IRR and IRS. The longitudinal comparison showed an age related GM loss in the hippocampal area over all groups (Fig. 3D). This age related GM loss was significantly reduced in the SRR mice (Fig. 3B) but not in the IRR mice (Fig. 3E).

**Discussion**

These results corroborated our earlier findings [2] and findings in human MR studies [7, 8], where increased hippocampal volume was associated with voluntary exercise. We can now specify this increase of hippocampal volume as a decelerated gray matter loss over time in voluntary exercising mice. We found no increase of hippocampal volume in voluntary running mice after hippocampal irradiation, an intervention which effectively inhibits hippocampal neurogenesis [5]. Moreover, non-exercising mice had higher hippocampal GM compared to irradiated non-exercising mice. Running had no effect on hippocampal GM in irradiated mice. These findings suggest an association of the plastic changes through voluntary wheel running and VBM-detected gray matter volume, which seem to be inhibited through irradiation.

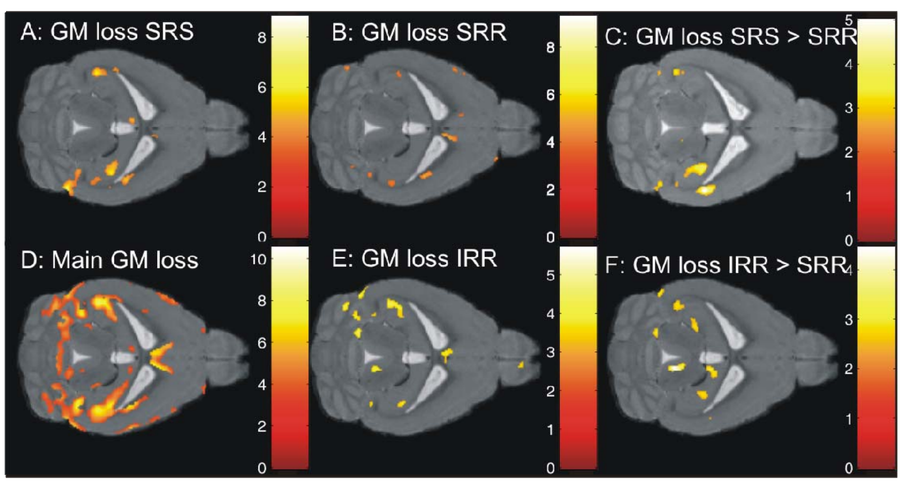


**Fig. 3:** Longitudinal gray matter (GM)-changes showing the GM-loss in non-radiated sedentary (SRS) (A), non-radiated runner (SRR) (B). Higher GM loss in SRS compared to SRR (C). Longitudinal loss of GM in all mice (D). GM loss in irradiated runner (IRR) (E) and higher GM loss in IRR compared to SRR (F).

**References**

**[1]** Pajonk FG et al. Arch Gen Psychiatry. 2010 67(2):133-43. **[2]** Weber-Fahr W et al. Proc ISMRM 2011 19:4182. **[3]** van Praag H et al. Nat Neurosci 1999 2:266–270. **[4]** Fuss J et al. 2010 Hippocampus 20:364–376. **[5]** Fuss J et. al. One. 2010 Sep 16;5(9). pii: e12769. **[6]** Kovacevic N et al. Cer.Cortex 2005 15(5):639-45. **[7]** Erickson K.I et al. Hippocampus 2009 19:1030–1039. **[8]** Chaddock et al Brainresearch 2010 13:58172-183.