

The influence of physical activity on the structure and metabolism of the mouse hippocampus - combining ^1H MRS and VBM at 9.4T

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Introduction

Voluntary wheel running in mice is known to effectively increase hippocampal neurogenesis and decrease cell death in the dentate gyrus within weeks [1,2]. Moreover, physical fitness is related to increased hippocampal volume in elderly and preadolescent humans [3,4]. Therefore, we asked how the known histological changes in wheel running mice are reflected by ^1H MRS and imaging at 9.4 T, eventually allowing to detect neuronal plasticity in vivo.

We assessed metabolic and structural profiles of the right hippocampus (HC), using in vivo single-voxel ^1H MRS and Voxel-Based Morphometry (VBM) on a 9.4T scanner equipped with a cryogenic mouse-brain coil.

Methods

24 C57BL/6J male mice were single-housed in Macrolon Type III cages, on a 12-h light-dark cycle. At the age of 9 weeks, 12 mice were given free access to a running wheel (diameter 11.5 cm). After 6 to 8 weeks of voluntary wheel running (~9-10 km/night) all mice were investigated with MRS and structural measurements.

Spectra were acquired using PRESS at an echo time of 10ms (TR = 4s) from a 3.2 μl volume located in the HC. Quantification was done with LCModel (Provencher, Canada) by fitting the in vivo spectra to phantom data of 16 different metabolites (Fig. 1a). Concentration values were referenced to an unsuppressed water signal acquired from the same voxel. The quantified metabolite concentrations were assessed in a GLM with group as factor and weight as covariate.

T_2 -weighted high resolution 3D-morphometric data were acquired using a RARE-Sequence with a resolution of 78x78x156 μm at TE=50ms. The complete segmentation of the mouse brains was performed in several steps, including brain extraction, a 2-step sequential individual segmentation with SPM8 using binary brain masks and output of the first segmentation as priors, template generation with DARTEL (Fig. 2a) and template-based individual segmentation [5]. The segmented and normalized-modified tissue class images were smoothed with 0.4mm Gaussian kernel and analyzed voxelwise with a second level two sample t-test over the whole brain and a correlation analysis of MRS-Data with the VBM-modified grey matter (GM) values masked over the hippocampus region [6].

Results

The MRS findings show a significant decrease of Glutamate (Glu) in the right hippocampus of the exercise-group ($p < 0.005$) (Fig. 1b). The animal weight and all other metabolite concentrations did not show any significant differences. The VBM over the whole brain revealed a significant cluster ($p < 0.001$ uncor., min. 100 voxels) of increased grey matter (GM) in the right hippocampus (Fig 2b). At this significance level no other differences were found (WM, CSF or $\text{GM}_{\text{Controls}} > \text{Sport}$) in any brain region. We then masked the GM-tissue maps with a brain atlas ROI from the right hippocampus and found a negative correlation between the GM volume and the Glu concentration in this side of the hippocampus ($p < 0.05$ ucor, Fig. 2c). The plot of the mean data over the significant cluster in the right hippocampus shows a good separation between the exercise- and the control-group (Fig 2d).

Discussion

Our data show that the increase in hippocampal volume by exercise that might be induced by neurogenesis can be detected with VBM methods in a well characterized mouse collective. Additionally, this study is a direct corroboration of a 16% total hippocampal volume increase in humans after a moderate exercise training over 12 weeks [7]. In analogy to our findings the human hippocampal increase showed no correlation with MRS metabolites, but hippocampal glutamate was not resolved there. The highly significant findings of reduced Glu in the exercise group and its correlation to the hippocampal volume need further investigation.

References

[1] van Praag H et al. Nat Neurosci 1999 2:266–270 [2] Fuss J et al. 2010 Hippocampus 20:364–376. [3] Erickson K.I et al. Hippocampus 2009 19:1030–1039 [4] Chaddock et al Brainresearch 2010 13:58172-183 [5] Zheng L et al. Proc ISMRM 2009 17:2897 [6] Kovacevic N et al. Cer.Cortex 2005 15(5):639-45 [7] Pajonk FG et al. Arch Gen Psychiatry. 2010 67(2):133-43

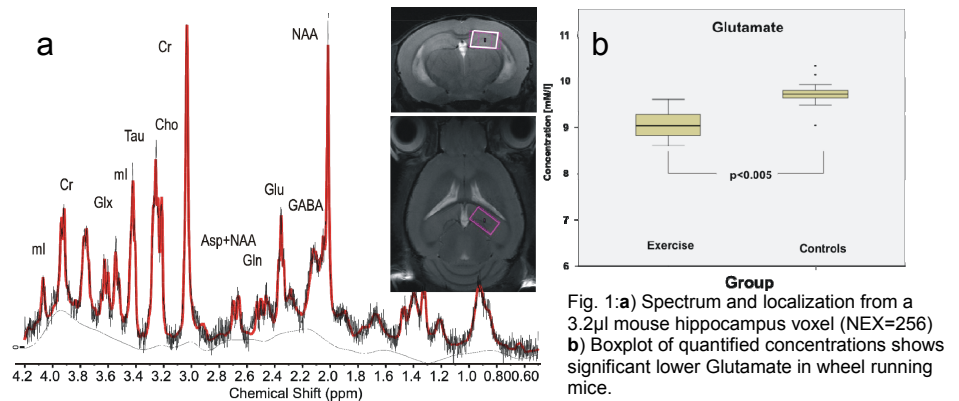


Fig. 1: a) Spectrum and localization from a 3.2 μl mouse hippocampus voxel (NEX=256) b) Boxplot of quantified concentrations shows significant lower Glutamate in wheel running mice.

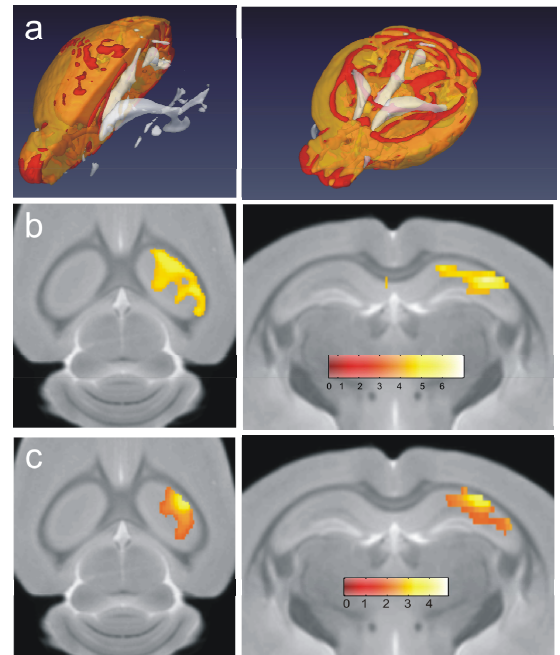


Fig. 2: a) DARTEL prior knowledge image from 7 high resolution images. b) Significant ($p < 0.001$ ucor) GM increase in runners vs. controls overlaid on a coregistered mouse atlas image [6]. c) Significant neg. correlation of GM with Glu in the hippocampus ($p < 0.05$, masked with hippocampus ROI). d) Regression of Glu with GM-mean over the significant cluster in the right hippocampus.