MRI-Detectable Changes in Mouse Brain Structure Induced by Voluntary Exercise

Lindsay S Cahill[1], Patrick Steadman[1], Christine L Laliberte[1], Patrick Macos[1], Jun Dazai[1], Jason P Lerch[1,2], Bojana Stefanovic[2,3], and John G Sled[1,2]
[1]*Mouse Imaging Centre, Hospital for Sick Children, Toronto, Ontario, Canada,* [2]*Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada,* [3]*Sunnybrook Research Institute, Toronto, Ontario, Canada*

Introduction. Understanding the role of exercise in changing brain structure and in improving memory function is important for human health. Recent studies have shown significant increases in volume in both the cerebral cortex and hippocampus in older adults that follow an aerobic exercise regime [1]. However, isolating the effect of exercise on brain structure can be challenging due to the variability among individuals (e.g. genetic factors, initial level of fitness). Experimental animal models allow for careful control of environmental factors and monitoring of voluntary exercise. Previous animal studies have looked at microscopic changes in selected regions using histology [2-5]. 3D MR imaging provides the advantage of unbiased, whole-brain analysis. The purpose of this study is to map, using high-resolution MR imaging in combination with deformation-based morphometry, the macroscopic changes in brain structure that occur in healthy mice that undergo voluntary exercise.

Materials and Methods. Forty healthy C57Bl6/J mice at 12 weeks of age were housed individually for four weeks in either a control or exercise group. Mice in the exercise group had continuous access to a running wheel with an odometer attached (distance ran was monitored daily). After four weeks, mice were anesthetized and a transcardiac perfusion was performed [6]. A multi-channel 7.0 T, 40 cm diameter bore Varian magnet was used to acquire anatomical images. A custom-built 16-coil solenoid array was used to image 16 samples concurrently. Parameters used in the scans were optimized for gray-white matter contrast: a T2-weighted 3D fast-spin echo sequence, with TR = 2000 ms, echo train length = 6, TE_{eff} = 42 ms, FOV = 25 x 28 x 14 mm and matrix size = 450 x 504 x 250, giving an image with 56 µm isotropic voxels. Total imaging time was 11.7 hours. An automated image registration-based approach was used to assess anatomical differences related to voluntary exercise. The registration resulted in deformation fields for each individual brain, which were used to calculate individual volumes from the segmented population average. The volume of 62 different structures, normalized to total brain volume, was assessed [7]. The cerebellum was further segmented into an additional 37 cerebellar structures. As well, voxel-by-voxel changes were evaluated over the entire brain. Cortical thickness was calculated as previously described [8].

Results and Discussion. In comparison to the control group, the mice in the voluntary exercise group showed a significant increase in the volume of two grey matter structures in the brain: the hippocampus and the stratum granulosum of the dentate gyrus (increases of 3% and 4% with a false discovery rate of <10% and < 20% respectively). Both structures showed a strong positive correlation between normalized structure volume and exercise performance, measured as the total distance each mouse ran over four weeks (**Figure 1**). The increased volume of the hippocampus and dentate gyrus can most likely be explained by the creation of new neurons, a process that is known to occur after wheel running in mice [4,5]. The voxelwise analysis revealed the change in the hippocampus to be bilateral and predominantly in the anterior hippocampus, consistent with recent findings in humans [9]. Moreover, the lateral ventricle and cerebral aqueduct were found to have a significant decrease in volume (decreases of 6% and 7% respectively with a false discovery rate of < 20%). Using the additional delineations of the cerebellum, it was possible to detect a trend towards increasing volume in the exercise group localized to the copula pyramis and the paramedian lobule. This finding is consistent with a histological analysis of the paramedian lobe in rats after physical exercise [2]. Finally, the mean cortical thickness of the exercise group was found to have a positive correlation with performance (**Figure 2**), consistent with findings from histology of increase thickness in the motor cortex of rats [3].

In summary, anatomical MR imaging in mice provides a method for studying macroscopic changes in the brain that can be attributed directly to voluntary exercise. The structural changes observed here in healthy mice are consistent with findings in humans that focused on diseased and ageing populations.

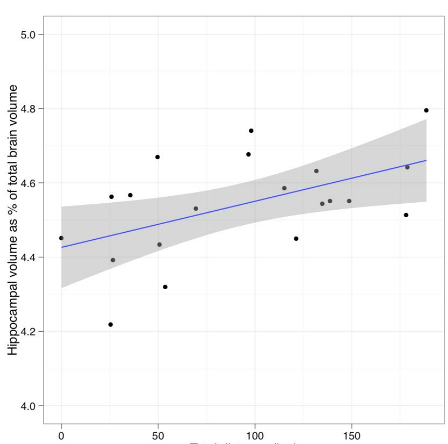

Figure 1. Scatter plot showing the hippocampal volume (% of total brain volume) of the exercise group with total distance run (km) (p=0.0182). The grey shaded regions are 95% confidence intervals.

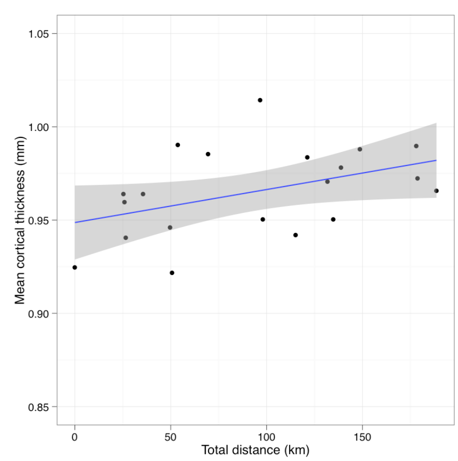

Figure 2. Scatter plot showing the mean cortical thickness (mm) of the exercise group with total distance run (km) (p = 0.055). The grey shaded regions are 95% confidence intervals.

References. [1] Thomas et al. (2012) Frontiers in Psychology, 86:1-9. [2] Black et al. (1990) PNAS, 87:5568-5572. [3] Anderson et al. (2002) Learning and Memory, 9:1-9. [4] van Praag et al. (1999) Nat. Neurosci., 2:266-270. [5] van Praag et al. (1999) PNAS, 96:13427-13431. [6] Dazai et al. (2011) J. Vis. Exp., 48:e2497. [7] Dorr et al. Neuroimage, 42:60-69. [8] Lerch et al. (2008) Neuroimage, 41:243-251. [9] Erickson et al. (2011) PNAS, 108:3017-3022.