Learning is necessary for training induced brain plasticity

J. P. Lerch[1], A. Badhwar[2,3], E. Hamel[2], and J. G. Sled[1]
[1]Mouse Imaging Centre, Hospital for Sick Children, Toronto, Ontario, Canada, [2]McGill University, Montreal, Quebec, Canada, [3] (contributed equally to this abstract)

Introduction. It is well established that brain structure is plastic and can reorganize in response to specific stimuli; however, it has only recently been recognized that these changes can manifest as volumetric differences detected on MRI [1-2]. We have previously shown in mice that five days of spatial memory training using a water-maze is sufficient to cause region specific local volume changes detected on MRI with the aid of image registration software [3]. Here we used a mouse model of Alzheimer's Disease (AD) with impaired spatial learning to test whether a capacity to learn is necessary for training induced volume changes to occur.

Mice and training. Fifteen 6-month old wild-type C57/Bl6 mice (WT) and 14 6-month old amyloid precursor protein transgenic mice (APP; J20 mouse line with neuronal overexpression of the Swedish ($670/671_{KM\rightarrow NL}$) and Indiana ($717_{V\rightarrow F}$) mutations of human APP [4]) were trained on one of two versions of the Morris Water Maze (MWM). In the spatial version the mice were tasked with finding a submerged platform based on distal visual cues, a task which is primarily dependent on the hippocampus and known to be impaired in AD [5]. In the non-spatial version of the MWM, the distal visual cues were removed but the platform marked with a flag; solving this task is simpler, primarily dependent on the striatum, and not expected to be impaired in AD [5]. Mice were trained for five days with six trials per day.

Imaging and analysis. Ten days after training, the mice were sacrificed, anaesthetized (65mg/kg sodium pentobarbital, ip), perfused through the heart with phosphate buffered saline (PBS, 30 ml, pH 7.4, 25˚C) followed by paraformaldehyde (4% PFA; 30 mL, 25˚C) plus 2 mM ProHance in PBS. Bodies, along with the skin, lower jaw, ears and the cartilaginous nose tip were removed. The remaining skull structures containing the brain were allowed to postfix in 4% PFA plus 2 mM ProHance at 4˚C for 12 hours. The skulls are then transferred to solution containing 1X PBS + 0.02% sodium azide + 2mM ProHance for 4 days at 15 °C. A multi-channel 7.0 Tesla MRI scanner (Varian Inc., Palo Alto, CA) with a 6 cm inner bore diameter insert gradient was used to acquire anatomical images of brains within skulls. Prior to imaging, the samples were removed from the contrast agent solution, blotted and placed into plastic tubes (13 mm diam) filled with a proton-free susceptibility-matching fluid (Fluorinert FC-77, 3M Corp., St. Paul, MN). Three custom-built, solenoid coils (14 mm diam, 18.3 cm in length) with over wound ends were used to image three brains in parallel. Parameters used in the scans were optimized for grey/white matter contrast: a T2-weighted, 3D fast spin-echo sequence with 6 echoes, with TR/TE= 325/32 ms, four averages, field-of-view 14 x 14 x 25 mm^3 and matrix size = 432 x 432 x 780 giving an image with 32 μm isotropic voxels. Total imaging time was 11.3 hours. The resulting images underwent a non-linear deformation algorithm to bring all brains into exact correspondence, and the Jacobian determinants of the deformation fields were used to measure local volume change [6].

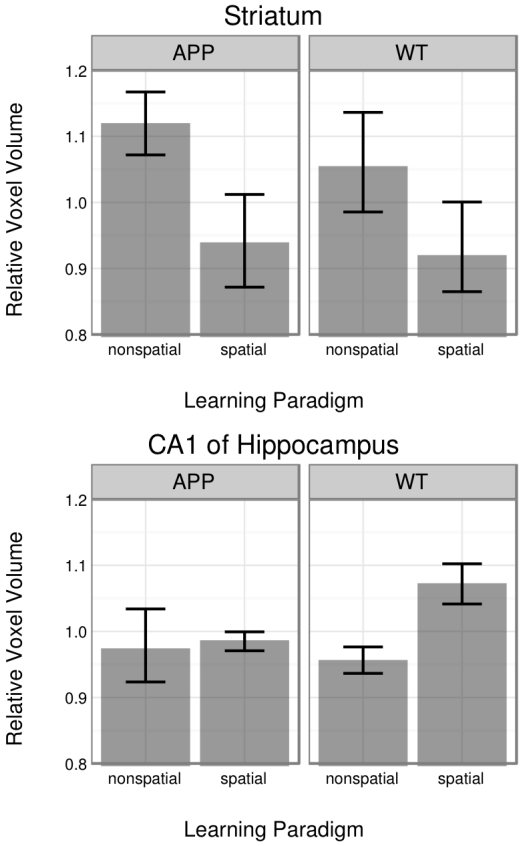

Fig 1. Mean and 95% confidence intervals for two voxels in the brain, separated by genotype.

Results. As hypothesized, WT mice trained on the spatial MWM showed volume growth in the hippocampus compared to the non-spatial MWM WT trained mice, which in turn showed relative enlargement of the striatum. The APP mice, on the other hand, failed to learn the spatial MWM and showed no enlargement of the hippocampus; results on the non-spatial MWM were, however, comparable to WT mice (see Fig 1 for plots illustrating two voxels).

Discussion. The data presented herein indicates that learning is a requirement for MRI detectable plasticity. Both WT and APP mice learned the non-spatial MWM and showed concomitant volume increases in regions of the striatum. Only WT mice learned the hippocampus dependent spatial MWM and showed hippocampal volume increases; APP mice, on the other hand, neither learned the spatial MWM nor featured hippocampal volume changes.

References. [1] Scholz et al., Nat. Neurosci, 2009. [2] Draganski et al., Nature, vol 427 (6972), 2004. [3] Lerch et al., ISMRM, 2008. [4] Mucke et al., J. Neurosci, vol 20 (11), 2000. [5] D'Hooge and De Deyn, Brain Research Reviews, vol 36, 2001. [6] Spring et al., NeuroImage, vol 35 (4), 2007.