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Using in-vivo MRI to study learning induced brain plasticity in adult mice trained on a spatial maze.

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Introduction – Several studies have demonstrated that brain shape is influenced by experience. For example training mice to navigate in the Morris Water Maze is associated with changes in neuroanatomy detected using fixed brain MRI after only 5 days of training (1). The time course of the changes, however, remains unknown. To elucidate the time-course of changes in neuroanatomy in response to learning we longitudinally imaged mice undergoing spatial navigation training. We used a navigation task as the learning paradigm wherein small manipulations of the experimental setup cause mice to use different cognitive strategies engaging distinct brain networks and thus leading to plastic changes in distinct locations.

Methods – S*ubjects*-48 C57B6/129Sv F1 hybrid mice were used in this study. Behavioral training started at 7 weeks of age. *Behavioral Testing*- The mice were trained in a spatial and stimulus response (S-R) version of the Barnes maze (BM) in addition to an untrained control group (20 spatial, 15 S-R, 13 control). In the S-R version of the BM mice learn to navigate using a local cue, a cognitive strategy thought to depend on the striatum (1,2). In keeping with the analogy introduced by Maguire and colleagues (3) we refer to those mice as 'bus mice' since their strategy is comparable to a bus driver following a routs indicated by landmarks. In the spatial version mice learn to navigate using distal landmarks and an internal cognitive map, which relies primarily on the hippocmapus (1,3). We refer to those mice as 'taxi mice' since this cognitive strategy is involved in successfully navigating a city's road network. Each mouse was scanned between 3 and 6 times starting up to 3 days before training and continuing for 4 weeks post training. All mice were trained for 5 consecutive days performing 6 trials per day. Altogether 229 brain volume data sets were acquired. *MRI acquisition*-All MRI's were obtained using a multi channel high-field (7T) MR scanner (Varian Inc., Palo Alto CA) (4). To investigate the time course of possible structural brain changes live imaging of up to seven anesthetized mice simultaneously using a FSE sequence (Echo Train-Length: 12, FOV: 3.5x4.2x2.1cm, TR: 1.8s, TE effective: 40ms, 125 µm isotropic resolution, duration: 2h45min). *Data Analysis*- The MRI scans were non-linearly aligned to a common average and further to a three dimensional atlas of the mouse brain with 60 structures identified (5). The resulting deformation fields for each individual brain were used to investigate local brain changes at a voxel level and the atlas registration to calculate individual structure volumes. All measure were normalized using the 'day 0' scan acquired before training commenced. For all analysis 'day 1' is the first day of training.

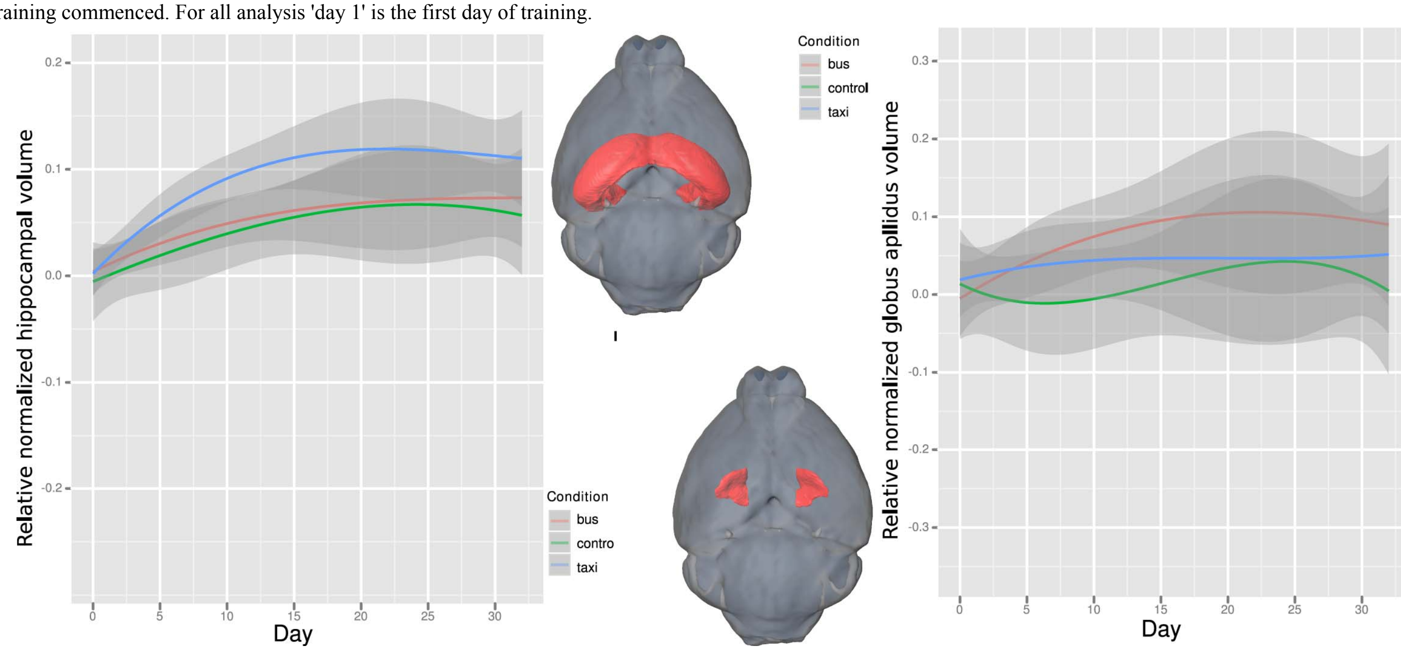

Fig. 1: Mice that learn to navigate using local cues -the bus mice doing route learning- show a marked increase in the relative size of the globus pallidus. Mice that learn to navigate using distal landmarks and an internal cognitive map –more similar to a taxi driver navigating a city- show a marked increase in the relative size of the hippocampus.

Results– Learning is associated with definite local brain changes that are detectable using live-imaging. These changes, detected as early as on the second day of training, occur in specific brain regions depending on the cognitive strategy determined by the experimental setup. Mice trained on the spatial version of the BM show a progressive 10% volume increase of the hippocampus during the first 15 days (training plus 10 days) (Fig.1). This gain is stable for the remainder of the experiment (another 20 days). A similar volume increase is found in the globus pallidus in mice trained on the S-R version of the BM (Fig.1). These increases are specific to the experimental condition, the globus pallidus changes in mice trained on the S-R but not in the spatial learning condition. Conversely the progressive volume increase in hippocampus in only found in mice trained on the spatial version of the task but the S-R version. The long lasting volume increases in the hippocampus and globus pallidus respectively are not the only changes observed during learning. For example the entorhinal cortex shows a progressive increase in local volume only in mice trained on the spatial version of the BM reaching a 8% volume increase at day 5. After training ended the entorhinal cortex volume returns to baseline within a week.

Discussion and Conclusion – Spatial learning independent of experimental setting is associated with a series of specific local structural brain changes. Different learning conditions are associated with a set of very distinct local changes. The changes are found in regions that have been demonstrated to be crucially involved in the particular navigation task: e.g. the hippocampus in spatial learning (3) and the basal ganglia in S-R learning (2). The structural changes observed are rapid and continue for a considerable period after training ended. The time course of local remodeling varies between regions. Whole brain live MRI is capable of detecting and characterizing these changes and is instrumental in unveiling the actual sequence of local changes within the brain as a learning system or deviation from normal found in disease.

References- 1)Lerch et al., NeuroImage (in Press, 2010) , 2) Bohbot et al., SFN (2007), 3) Maguire et al. PNAS (2000), 4) Bock et al., Magn Reson Med (2005)**,** 5) Dorr et al. *Neuromiage* 42: 60-69 (2008)