Can preexisting differences in neuroanatomy predict training performance? An in-vivo MRI study of adult mice trained on a spatial maze.

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Introduction – In the famous London taxi driver study Maguire and colleagues found that some hippocampal regions are significantly larger in London taxi drivers than in matched controls (1). These local anatomical differences are likely caused by the extensive navigation experience as 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 (2). What, however, is the influence of preexisting anatomical differences on subsequent learning performance. Navigational experience leads to local volume increases in the hippocampus but what if the taxi driver in question had a larger hippocampus to start with? Did he/she learn to navigate through the streets of London quicker? To study the effect of prior differences in neuroanatomy on 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 regions.

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) versions of the Barnes maze (BM) in addition to an untrained control group (20 spatial, 15 S-R, 13 control). 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. The 48 scans acquired prior to training were used in this study. 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 (2,3). In keeping with the analogy introduced by Maguire and colleagues (1) 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 (1,2). We refer to those mice as 'taxi mice' since this cognitive strategy is involved in successfully navigating a city's road network. Over the course of the 30 trials mice manage to navigate the maze quicker and we fitted a decay curve to the 'time to target' measure to characterize learning performance and used the decay rate as outcome measure of learning performance. Smaller decay rates indicate better learning (faster improvement). Values greater than 1 describe a mouse that does not improve over the course of the training. *MRI acquisition*-All images were obtained using a multi channel high-field (7T) MR scanner (Varian Inc., Palo Alto CA). 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, resolution 125 µm isotropic, duration: 2h45min) (4). *Data Analysis*- The MRI scans were non-linearly aligned to a common average. The resulting deformation fields for each individual brain were computed and used to investigate local brain changes at a voxel level.

Results– The learning performance of mice is associated with preexisting local brain variance detectable using live-imaging. The specific region where prior local anatomical variance is predicting subsequent learning performance depends on the cognitive strategy that the mouse will have to use as determined by the experimental setup. Mice that show preexisting larger local volume in the dorsal striatum will learn the S-R version of the BM better (p=0.0005 uncorrected). Larger local volume in the dentate gyrus, entorhinal cortex, fornix and amygdala is associated with subsequent better learning performance (q<0.05, FDR corrected), local volume increase in the CA3 filed of the hippocampus is associated with poorer learning performance (q<0.01, FDR corrected).

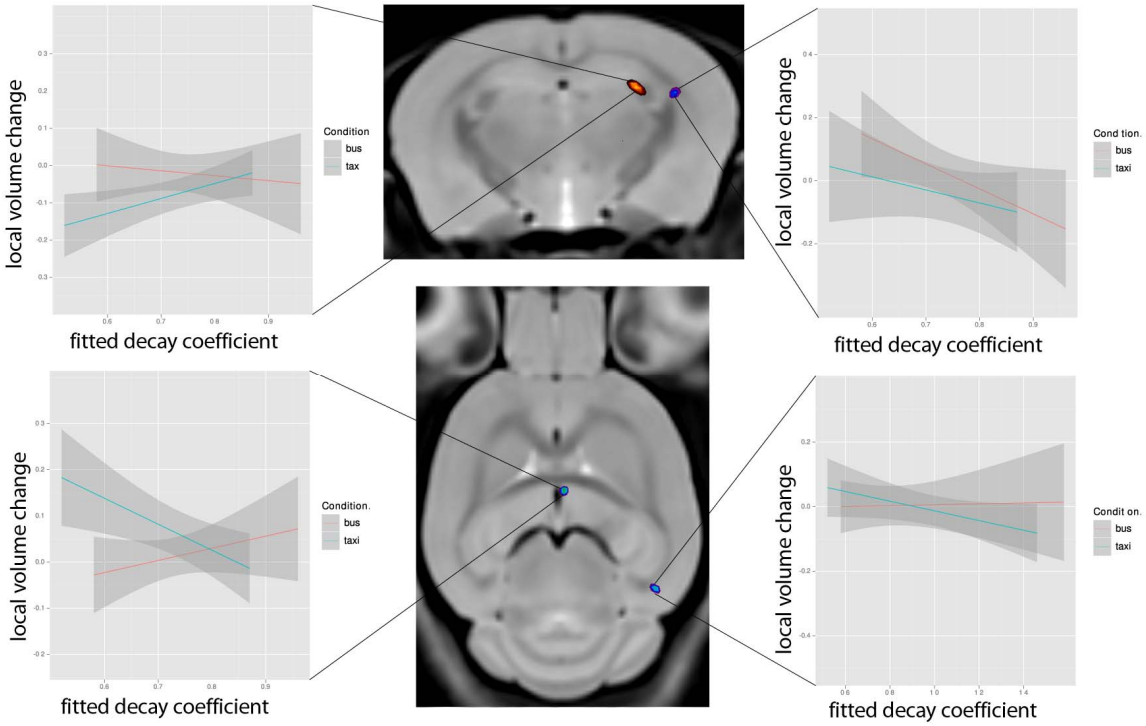

Fig.1: Examples of four regions were preexisting local volume changes show strong relationships with subsequent learning performance in the mice learning to navigate using local cues and mice that learn to navigate using distal landmarks and an internal cognitive map. The statistical t-maps are overlaid onto anatomical images and thresholded at |t|>4.

Discussion and Conclusion – Local brain size predicts subsequent learning performance. What brain region is critical depends on the characteristics of the task to be learned: striatum for S-R learning, hippocampus, dentate gyrus, fornix and amygdala for learning a spatial cognitive map, all regions that have been demonstrated to be crucially involved in the particular navigation task (1,2,3). The source of the preexisting variance remains uncertain. All mice are genetically identical and raised in identical environments. However, even though the preexisting anatomical differences are small, much smaller then the anatomical changes associated with learning the different tasks (2), they exert a strong influence on learning performance. Whole brain live MRI is capable of detecting and characterizing local anatomical differences and is instrumental in studying brain behavior relationship and investigating the influence of preexisting local anatomical differences on behavioral performance, the changes in anatomy caused by experience and the possible interaction between the two.

References- 1)Maguire et al. PNAS (2000), 2)Lerch et al., NeuroImage (in Press, 2010) , 3) Bohbot et al., SFN (2007), 4) Nieman et al., Magn Reson Med (2005)