Short term learning induced white matter plasticity in the fornix

Shir Hofstetter[1], Ido Tavor[1], Shirmrit Tzur-Moryosef[1], Tamar Blumenfeld Katzir[1], and Yaniv Assaf[1]
[1]*Tel Aviv University, Tel Aviv, Israel, Israel*

Introduction: MRI is a potent technique for the *in-vivo* measurement of neuroplasticity. Several studies have shown morphological modification in cortical thickness after learning a new skill using T1-weigthed imaging, a common method that provides a good contrast of the tissues macro-structure *(1)*. Diffusion tensor imaging (DTI) is sensitive to the micro-structure, and can offer more detailed information on the underlying structural processes of plasticity. Indeed, several studies found changes in white matter after acquiring a new skill like juggling.*(2)* Previous studies in our lab discovered that a short term spatial learning, both in humans and rats, can lead to changes in diffusion parameters. MD decrease was found in the hippocampus after 2 hours of training in a car race game (Figure 1). Rats undergoing Morris water maze (MWM) training for different durations showed similar MD decrease in the hippocamps and septum.*(3)* In line with these results, we aimed to investigate structural changes in the fornix of humans and rats, as it is the main hippocampal projection and is known to be involved in memory processes.*(4)* However, in order to investigate changes in this fairly small tract across subjects, the alignment of the whole brain images formerly used was not sufficient. We therefore applied a common method for the studying of white matter: tract based spatial statistics (TBSS).*(5)*

Figure 1: MD decrease in the hippocampus after 2 hours of car racing game. (n=17, p<0.005)

Methods: ***Human study:*** 29 subjects underwent two series of DTI scans, separated by a 2 hour spatial learning task. The task included 16 laps of the same car game track (Electronic Arts©). Their objective was to memorize the track and achieve better lap times.
DTI analysis: Resolution = 2.1mm^3. DTI analysis computed the MD (mean diffusivity) and FA (fractional anisotropy). TBSS was employed on FA maps from both scans. MD maps were analyzed by applying the same spatial transformation that was used on the FA images.
Rats studies: 2 groups (age of 4m) were trained on a conventional Morris water maze (MWM) for a different duration: ***1***. Group of 22 rats underwent 2 scans one week apart, and trained in-between for 5 days on MWM.(R1) ***2***. Group of 19 rats underwent 2 scans separated by 1 day of MWM training. (R2)
DTI analysis: *R1:* Resolution: 0.2*0.2 *1.2 mm*, 12 slices. R2*: Resolution 0.2*0.2 *0.8 mm, 21slices. Analysis of both groups included extraction of MD and FA maps. Maps were normalized to a rat template using SPM2 (UCL, London, UK). Using TBSS a skeleton was created on the mean FA image. FA and MD values were projected into the skeleton.
Statistical analysis of both rats and humans learning groups was restricted to the fornix using a mean mask, with FSL's "randomize" program carrying permutation tests, and the statistical images thresholded using TFCE*(6)*. GLMs were applied in order to detect differences between the 2 conditions and for correlation analysis.

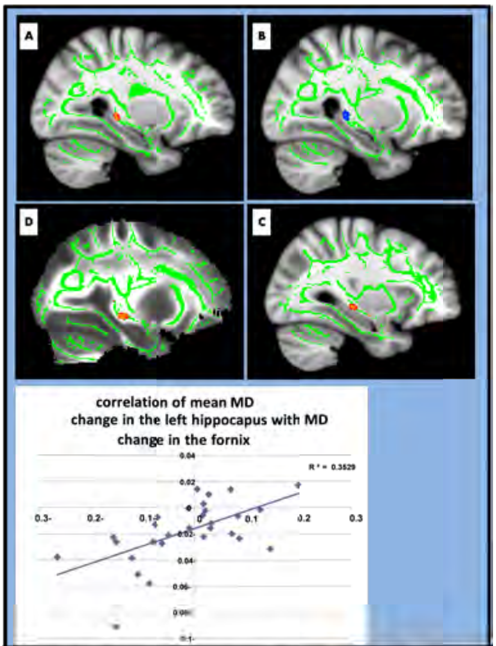

Figure 2: Human group results. A. FA decrease. B. MD increase. C. MD decrease. D-E. Correlations of MD change in the hippocampus with MD change in the fornix. (p<0.05 for display purposes.)

Results: ***Human group***: Voxel based statistics at p<0.01 and cluster size ≥ 5 revealed decrease in FA values (p=0.002 in most significant voxel) and a mixed pattern of change in MD values (p= 0.003 in most significant voxel). The previously found hippocampal MD decrease is positively correlated with changes in MD in the right fornix (r= 0.594, p<0.001) (Figure 2).
Rats groups: Both groups showed decrease in MD (p<0.05, corrected). Changes in MD in the hippocampus was correlated with MD changes in the fornix of rats undergoing 1 day of MWM (p<0.05 corrected, r=0.808). Alternatively, in rats undergoing 5 days of MWM, the hippocampal MD change was correlated with FA changes in the fornix (p<0.001, r=0.538) (Figure 3).

Discussion: This work provides the first indication of white matter plasticity in the fornix following a spatial learning task in both humans and rodents. It appears that structural changes in the white matter can occur in short time scales and can be detected with DTI. Results found in the fornix are complimentary to the hippocampus, the fornix's origin. Not only that both structures are involved in this task, the extent of change they undergo is connected.

References:1. B. Draganski et al., Neuroplasticity: changes in grey matter induced by training., *Nature* **427**, 311-2 (2004).2. J. Scholz, M. C. et al, Training induces changes in white-matter architecture., *Nature neuroscience* **12**, 1370-1 (2009).3. T. Blumenfeld-Katzir, et al, Diffusion MRI of structural brain plasticity induced by a learning and memory task., *PloS one* **6**, e20678 (2011).4. R. J. Sutherland, A. J. Rodriguez, The role of the fornix/fimbria and some related subcortical structures in place learning and memory., *Behavioural brain research* **32**, 265-77 (1989).5. S. M. Smith et al., Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data., *NeuroImage* **31**, 1487-505 (2006).6. S. M. Smith, T. E. Nichols, Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference., *NeuroImage* **44**, 83-98 (2009).

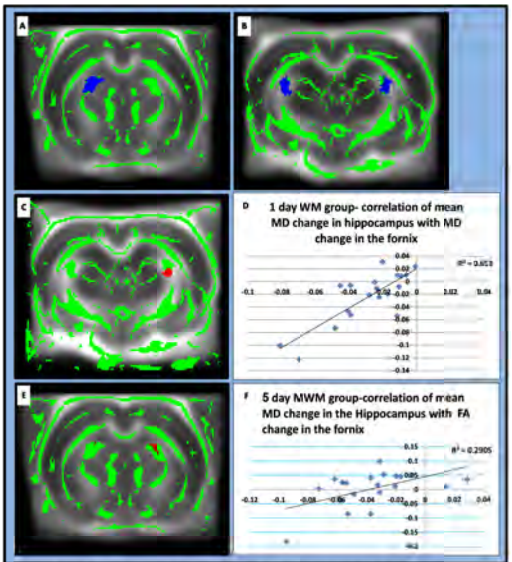

Figure 3: Rats groups results: A. MD decrease in R2. MD decrease in R1. C-D. Correlations of MD change in hippocampus with change in MD in the fornix after 1 day of MWM. (P<0.05 corrected, n=19). E-F. Correlation of MD change in hippocampus with changes in FA in the fornix after 5 day of MWM (P<0.005, n=21)