The Evolution of Short-Term Plasticity in the Rat Hippocampus

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Introduction

Structural neuroplasticity is a dynamic process underlying the ability to learn and adapt to new environmental situations. DTI, a diffusion MRI framework sensitive to tissues microstructure, was previously shown to be a valuable method in exploring plasticity in short time scales. Former studies have found changes in diffusivity following short tasks of only hours[1], but the initial temporal and spatial progression of this process is yet to be discovered. In the current study we used the Morris water maze paradigm, a well-known method to study learning and memory in rodents and a hippocampal dependent task[2], to explore the evolution of structural plasticity in the hippocampus of rats at different stages of the learning process.

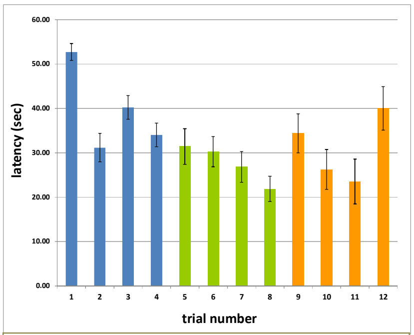

Figure 1: Results of the Morris water maze training: average latency in each trial (trials 1-4, *N*=55; trials, 5-8 *N*=37; trials 9-12, *N*=19)

Methods

Behavioral paradigm: In short, the Morris water maze paradigm involves finding the location of a hidden platform in a round pool. In each trial the rat enters the pool from a different quadrant and has limited time to swim and find the hidden platform. In the current study 55 adult rats (12-15 weeks) were divided into three groups, each group completed a different number of trials in the maze: 1 block- 4 trials (B1, *N*=18), 2 blocks- 8 trials (B2, *N*=18) and 3 blocks- 12 trials (B3, *N*=19). Time interval between blocks was 45 minutes.

Scanning protocol: Rats were scanned with a DTI protocol 2-3 days before the task and 45 minutes following the last maze training (matrix size: 128X128, 32 directions, 2 b0, repeated 3 times). DTI was calculated using Explore DTI[3]. Images of mean diffusivity (MD) were normalized to a rat template using SPM8 (UCL, London, UK). For each rat a normalized MD was calculated as the fraction between the MD obtained from the second scan divided by the first baseline scan. The logarithm of these values was fitted to a linear regression model with no intercept and the number of repetitions served as the covariates. Regression and statistical analyses were calculated in MATLAB.

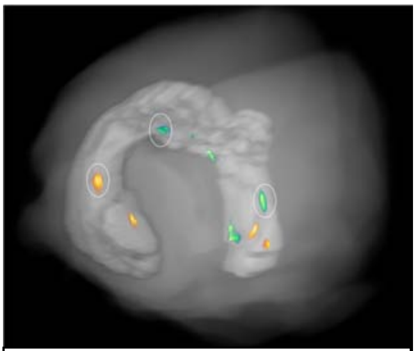

Figure 2: Regions showing gradual change in the slope of regression. Green color scale present increase in slope and red scale present a decrease. Marked In circles are regions further analyzed in figure 3.

Results

The time needed to reach the hidden platform (latency) was reduced as the learning progressed (paired *t*-test between the first and last trial, calculated for each group, $p<0.001$). Regression analysis revealed few cores where the slope (β) of the regression was changing gradually (Figure 2). These variations in slope depict a continuing change in the difference between the three groups. This difference diminishes progressively from the inner to the outer surface of the core. K-means clustering analysis on few of these regions revealed a circular and laminar order (Figure 3: B, C, F). The mean percentage of change in MD was extracted from the laminas for each group (Figure 3: A, D, E). As shown in figure 3 the extent of change in MD reduces from the inner to the outer borders of the regions. A two-way between (clusters and regions) ANOVA analysis on the mean slope of the regression found a significant interaction and main effects ($p<0.0001$).

Discussion

The results of the current study provide a first demonstration of the progression of structural neuroplasticity at different stages of a learning process and exposure to a novel experience. Results show that the extent of change the tissue undergoes throughout the new training is dynamic, perhaps due to a change in the function of the underlying network during the experience or as a result of the time scale of the diverse biological processes involved in structural plasticity. In addition, a spatially ordered transformation was observed, showing maximum change in the core of some regions that decreases gradually to the margins. However, the pattern of the change varies between regions, suggesting a diverse effect of training along the hippocampus. Furthermore, results provide another confirmation of the power of MRI, and DTI in specific, as a tool to study neuroplasticity in the behaving adult brain, and its sensitivity to immediate modifications occurring in the tissue.

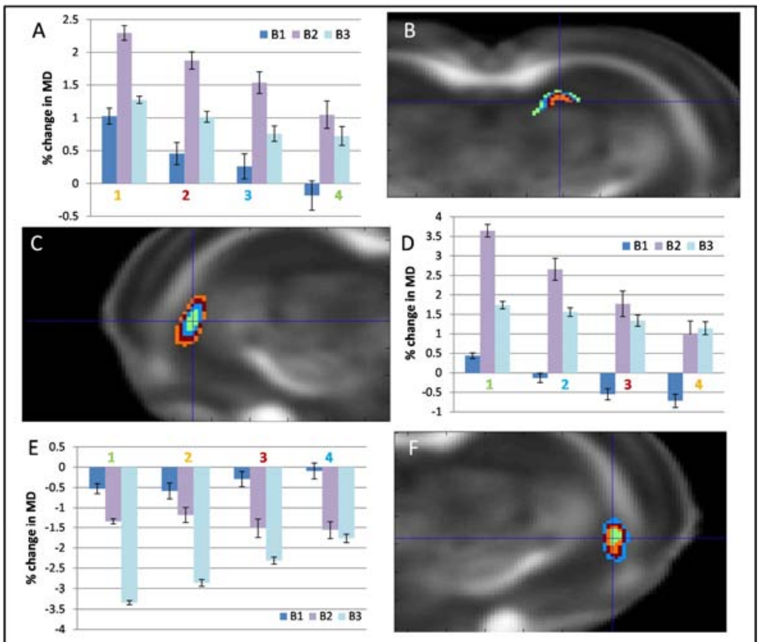

Figure 3: Clustering analysis of regions found in regression analysis (B, C, F). Each region was separated into 4 clusters. Percentage of change for each group was extracted for each cluster (A, D, E).

References: 1. Sagi Y, Tavor I, Hofstetter S, et al. Learning in the Fast Lane: New Insights into Neuroplasticity. *Neuron*. 2012;73(6):1195–1203. 2. D'Hooge R, Deyn PP De. *Applications of the Morris water maze in the study of learning and memory.* 2001:60–90. 3. Leemans A, Jeurissen B, Sijbers J and JD. ExploreDTI: a graphical toolbox for processing, analyzing, and visualizing diffusion MR data. In: *17th Annual Meeting of Intl Soc Mag Reson Med*. Hawaii, USA; 2009:3537.