The dynamics of short-term plasticity through water maze training

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Background: Diffusion MRI is sensitive to the microstructure of the tissue and enables the study of structural plasticity in short time scales of only hours[1]. However, the initial temporal and spatial progression of this process is still unrevealed. Here we used the Morris water maze paradigm to explore: **A**. the evolution of plasticity at different stages of the learning process; **B**. the effect of the overall time of the task on these changes.

Methods: To answer our first objective 3 groups of rats completed different number of blocks in the maze: 1-3 blocks, each comprised of 4 trials (**G1**; B1 *n*=15; B2 *n*=16; B3 *n*=18). Time interval between blocks was 45 minutes. The effect of overall time was explored with two additional groups of rats that completed 2-3 blocks (**G2**; B2 *n*=9; B3 *n*= 9).). Time interval between blocks was 2 hours. 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[2]. Images of mean diffusivity (MD) were normalized to a rat template using SPM8 (UCL, London, UK). The spatial pattern of structural change in G1 was calculated using a regression analysis: 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 using MATLAB.

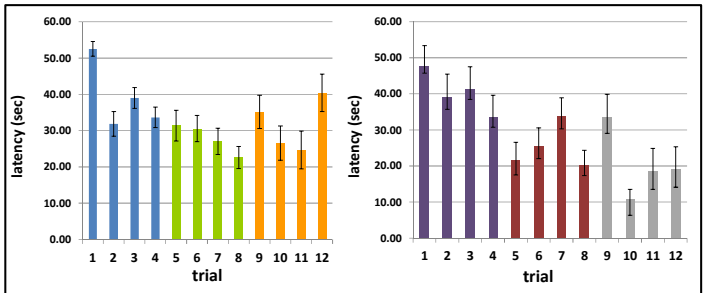

Figure 1. Average latency to reach the hidden platform. **A.** G1: Trials 1-4, *n*=49; 5-8, *n*=34; 9-12, *n*=18. **B**. G2: Trials 1-4, *n*=18; 5-8, *n*=18; 9-12, *n*=9

Results: Time to reach the hidden platform (latency) reduced as the learning progressed (paired *t*-test, p<0.05, Figure 1). Analysis of G1: a three (blocks) by two (scan time: pre-post training) mixed design ANOVA found a main effect of training in several regions (p<0.05, FDR corrected). Regression analysis showed a gradual change in slope (β) in several regions that represents a continuing change in the difference between the three groups. Clustering analysis discovered a circular and laminar order (Figure 2), where the averaged decrease in MD is reduced from the inner to the outer borders. A two-way (blocks and laminas) ANOVA found a significant interaction and main effects of these factors (p<0.0001). Analysis of G1 and G2: three-way mixed ANOVA (blocks (2-3) and interval time with repeated measures of scan time) found a main effect of training (p<0.005, cluster>20) in several regions as were found in G1 analysis, showing the same pattern of decrease in effect as number of trials progress (Figure 3). However, an interaction between scan time and the time interval (p<0.005, cluster>20) was also found in some regions, indicating that the overall time of the experience may also influence the induced change in the tissue, together with the number of trials in the task.

Conclusions: Results provide a first demonstration of the progression of structural neuroplasticity at different stages of a learning process and the exposure to a novel experience. Few minutes of training can cause changes in the tissue, and the extent of this effect modifies through the progression of the training. Moreover, it seems some regions are also influenced by the overall time of the experience. It seems that the process of structural changes, as revealed with diffusion MRI, is very dynamic, perhaps due to changes in the function of the underlying network during the experience or as a result of the time scale of the diverse biological processes involved. Finally, these findings support the role of diffusion MRI as a tool in the study of neuroplasticity and its sensitivity to locate and identify immediate changes in the tissue.

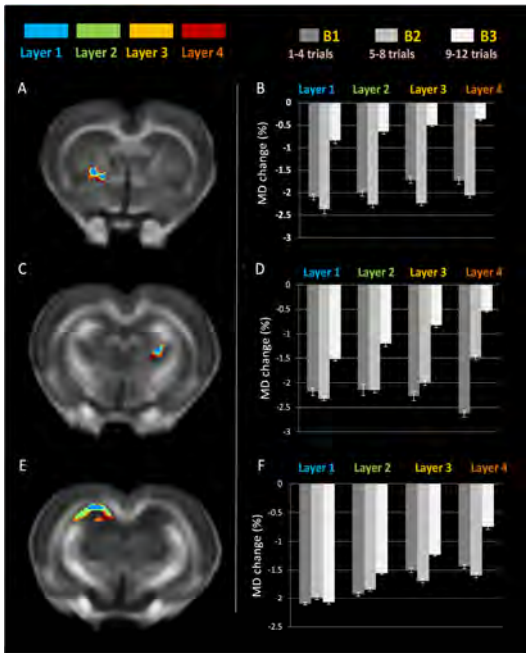

Figure 2. Layers organization in regions that show significant change in MD in G1 (p<0.05, corrected). Main effects and interaction between groups and layers was found in all regions (p<0.001): **A-B**. Globus Pallidus. **C-D**. Thalamus VPM. **E-F**. Hippocampus

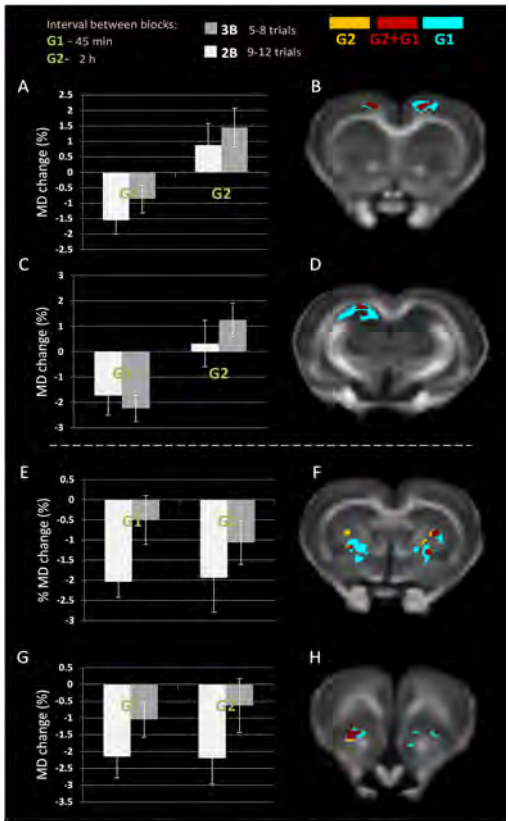

Figure 3: Results of mixed ANOVA (blocks by interval time by scan time). Interaction between interval time and scan time (pre-post training): **A-B** Motor cortex; **C-D** hippocampus. Results of main effect of training: **E-F** Globus pallidus; **G-H** nucleus accumbence. Significant clusters found in this analysis are overlaid on regions that show significant effect of training in G1 analysis.

Refecrences: 1. Sagi et al., neuron, 2012. 2. Leemans et al., 17th Annual Meeting of ISMRM, 2009.