Short-term learning induced plasticity visualized with diffusion MRI

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Introduction:

Plasticity in the adult brain following learning procedure is commonly attributed to functional plasticity- changes in synapse strengths, while structural plasticity such as synaptogenesis and neurogenesis are believed to be restricted to the hippocampus. Nonetheless, these are no longer considered as the exclusive ways of the brain to consolidate new memories. Structural plasticity involving neurons processes- axons and dendrites, glia cells and other regions beside the hippocampus is gradually gaining vast interest.
However, functional and structural plasticity are linked, the microstructure of the brain resembles its functional mapping. Most of the anatomic findings related to cognitive behavior are based on locally restricted and invasive methods such as brain lesions and electrophysiology. Rather, diffusion tensor imaging (DTI) is well established for microstructural characterization of the brain. However, most of the DTI studies in cognitive behavior focus on pathology and aging. Few MRI studies deal with plasticity induced by long term learning such as practice of musicians and taxi drivers [Imfeld, 2009; Maguire, 2006]. The work presented here seek for direct correlation between short-term learning and plasticity, while using the DTI parameters- apparent diffusion coefficient (ADC) and fractional anisotropy (FA) in order to characterize both white and gray matter changes.
Rats were scanned by MRI before and one day after a short version of Morris water maze (MWM) task. We used a one-day version of the MWM, which was first developed to deal with the estrus cycle in female and proved to show robust memory retrieval the day after [Warren, 1997; Smith, 1997]. Our main question is whether DTI is susceptible enough to observe structural plasticity after just few hours of learning paradigm and to locate the origin of memory processing.

Methods:

23 male wister rats (ages 3 months) were examined in this study and underwent two MRI scans (7T MRI system. Bruker, Germany). The rats were scanned before performing the one-day MWM [Smith, 1997] and the day after. The task comprises of spatial task acquisition- twelve trials, organized into three blocks with hidden and fixed platform , one probe trial- without platform and three non-spatial cued trials- while the platform is visible and non-fixed. The latencies and distances to reach the platform and the percentage of time swimming in each quadrant were recorded.
The MRI protocol included a DTI acquisition with diffusion-weighted spin-echo echo-planar-imaging (EPI) pulse sequence with the following parameters: TR/TE = 4500/22ms, Δ/δ=10/4.5ms, 4 EPI segments and 16 non-collinear gradient directions with b of 1000s/mm^2. 21 slices of 0.8 mm thickness and in-plane resolution of 0.2x0.2mm^2. Image analysis included DTI analysis using Matlab in-house software of the DWI-EPIs to produce for each rat FA, ADC maps. For statistical comparison between rats we used a voxel-wise approach where each rat brain volume was co-registered and normalized with Paxisons and Watson stereotactic atlas and included a registered template b0 and FA images. Following normalization, a paired t-test was performed on a pixel-by-pixel basis for each of the groups between the first and second MRI examinations.

Results:

The rats showed significant improvement in the spatial memory-as manifested by decreased swimming time in the three consecutive blocks and greater time spent in the training quadrant during the probe trial (Fig D, E). The paired statistical parametric maps revealed a highly significant ADC decreases in gray matter regions- middle striatum (caudate-putamen) and motor cortex (Fig. A), less significant decrease depicted in the substantia nigra (Fig. B). FA decrease depicted in gray matter region- rostral striatum (Fig. C) and an increase in white matter region- the cingulum bundle (data not shown).
It should be noted that, in contrast to previous studies, less significant ADC decrease was found in the hippocampus [Blumenfeld K, 2008].

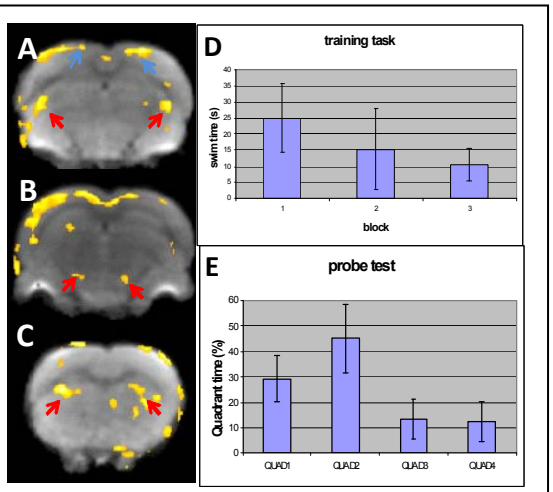

Fig. A-C: Coronal sections demonstrating changes in DTI parameters following MWM procedure. (A) ADC decrease in the medial striatum (red arrows) and visual motor cortex (blue arrows), (B) ADC decrease in the substantia nigra reticulata (n=19, p=0.005)
(C) FA decrease in the rostral striatum (n=19, p=0.005)
Fig. D,E: MWM performance. (D) Spatial task acquisition as measured by time to reach the platform.
Each point represents the mean (+/- standard error of the mean ,s.e.m.) of each group averaged over four trials. (E) Performance during the spatial probe trial. Each bar represents the mean (+/- s.e.m.) of the percentage of time in each quadrant, n=19.

Discussions & Conclusions:

The rats learned the task well and demonstrated large standard deviation between subjects, compared to previous study which used the MWM standard protocol [Blumenfeld K, 2008]. Assumingly, this is due to the challenged protocol comprising 16 trials in just 3 hours.
Following spatial learning paradigm, we would expect plasticity to occur in the hippocampusas the hippocampus is the funnel of new memories and their consolidation in the brain, specifically spatial memory. However, our main observations concentrate in the striatum, substantia nigra, motor cortex and cingulum. The results which revealed FA increase in the cingulum bundle implies changes in the arrangement of the fiber system. The change may be a manifestation in the number and/or density of fiber tracts as featured by axon and myelin composition, respectively.
FA and ADC decrease in striatum-related gray matter, suggests denser tissue with less organization (e.g. synaptogenesis and glia hypertrophy/hyperplasia). Notably, the striatum, substantia nigra and cortex areas are all associated with motor control. Additionally, the striatal system mediates acquisition but is not a site of long-term storage, corresponding to our short-term learning paradigm.
Lesions in cingulum bundle- in which the FA was increased, previously demonstrated spatial deficit in the MWM. All above regions correspond to previous related studies, thus validate our experimental approach, which claims that DTI parameters are sensitive to tissue changes in the brain induced by memory and learning paradigm.
Future work will include performing histological analysis of various cellular markers at the corresponding regions to elucidate the anatomic basis of these results.

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