Imaging experience-dependent changes in white matter microstructure in rats

J. Scholz[1], C. Sampaio[1], S. Mchugh[2], D. Bannerman[2], A. Khrapichev[3], N. Sibson[3], and H. Johansen-Berg[1]
[1]FMRIB Centre, Oxford, United Kingdom, [2]Experimental Psychology, Oxford, United Kingdom, [3]Gray Institute for Radiation Oncology & Biology, Oxford, United Kingdom

Introduction

Plasticity is an intrinsic property of the central nervous system that is present not only during development but throughout the life of the organism. Environment, experience and learning can alter the brain structure through different processes such as dendritic [1] and neuronal restructuring [2] in grey matter, and altered cortico-cortical wiring [3] and myelination [4] in white matter. Non-invasive techniques available in humans, such as MRI, can, however, not distinguish between different types of cellular changes. Thus, correspondence of MRI and histology in the context of experienced-related changes in the adult brain has to be established in a suitable animal model. Here we are especially interested in experience-related white matter changes, such as myelination and changes in axon calibre in response to a spatial memory task, i.e. Morris Water Maze (MWM). We hypothesize that fractional anisotropy (FA) of WM regions related to spatial navigation increases in animals that have learned a spatial reference memory task.

Methods

Animals: 3 groups of 8 male adult hooded Lister rats each. The MWM group received 4 training trials a day for 6 days. The Yoked group was matched for physical exercise, but did not learn (no hidden platform), The Caged group remained in the cage at all times. The MWM task required the animal to learn the location of a platform submerged in a pool of opaque water.

Acquisition: 3 batches of 3 post mortem brains each (one from each group) were scanned on a 7 T animal MRI scanner. Brains were perfusion fixed and placed in 4% PFA until the scanning day. Diffusion-weighted images (30 directions, 40 slices, thickness 0.5, resolution 0.26 x 0.26 mm) and 4 images with no diffusion weighting were acquired.

Analysis & Statistics: The tensor fit was performed with FSL's dtifit. Brain masks were created on basis of mean diffusivity images. A modified version of tract-based spatial statistics (TBSS) [5] was applied to the pre-processed data. Briefly, an initial study-specific template was generated by aligning all FA maps to midpoint. Then all FA maps were aligned to the template with affine transformations and averaged to generate the mean FA image from which the white matter skeleton was extracted. The skeleton was thresholded at an FA value of 0.35 to contain only the major tracts, shown in red-yellow on top of mean FA map (Fig. 2). Finally the FA values of the tract centres were projected onto the skeleton for each rat brain and fed into statistical analysis. Permutation testing with a cluster threshold of t=2 and 5000 permutations was used to determine corrected p-values.

Results

All animals improved their performance over the twenty-four trials (Fig. 1). One-way repeated-measures ANOVA analysis revealed significant differences between the first and last trial for the MWM group ($F(23, 161) = 10.738$; $p < 0.001$).

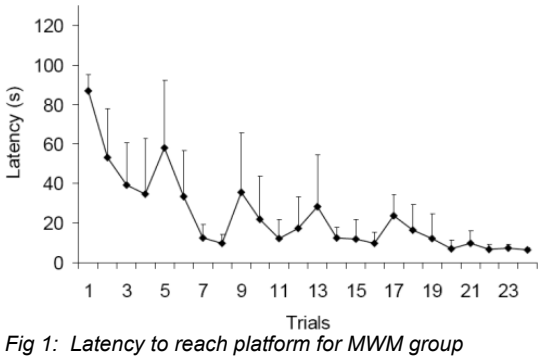

Fig 1: Latency to reach platform for MWM group

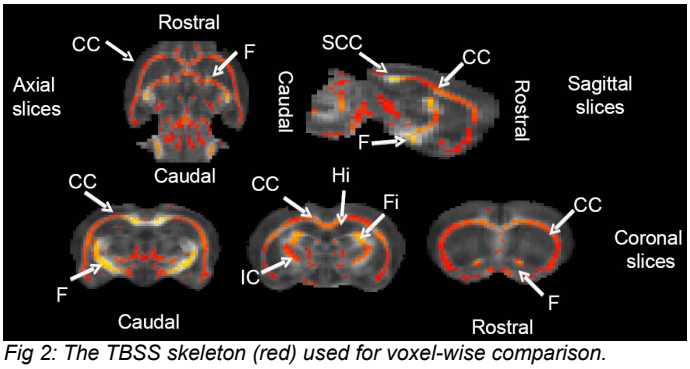

Fig 2: The TBSS skeleton (red) used for voxel-wise comparison.

To our knowledge this is the first application of TBSS to rat diffusion data. After several adjustments we were able to generate a white matter skeleton including the major fibre pathways. Statistical comparison yielded no significant group differences. However, we found a trend for MWM + Yoked > Caged ($t_{max} = 5.60$, uncorrected $p < 0.01$).

Conclusion

We successfully adapt TBSS to rat brain diffusion data. To our knowledge this is the first study to use TBSS analysis successfully with post-mortem rat brains. Although, at this stage, the group sizes are relatively small, the first statistical results are encouraging and support the hypothesized trends. The final objective of this study is to compare histology with the neuroimaging results and to identify imaging markers that correspond to specific histological processes.

References

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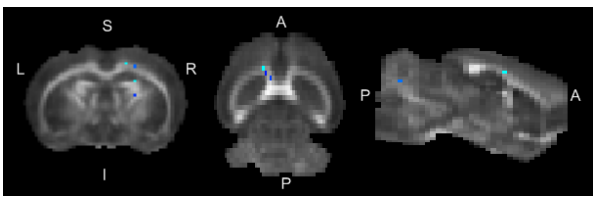

Fig. 3: Increased FA in MWM + Yoked > Caged. Blue voxels represent t-scores (dark to light blue, t=4 to t>5.6)