MRI Correlates of Dendrite Abnormalities in the MeCP2-A140V Mouse Model of Rett Syndrome

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Introduction

Rett syndrome is a neurodevelopmental disorder affecting grey matter that is characterized by slowing of development at 6-12 months, loss of purposeful use of hands, deceleration of head growth, difficulty walking and intellectual disability [1]. Mutations of the gene MeCP2 have been shown to cause Rett syndrome and are associated with other neurodevelopmental disorders such as autism and X-linked mental retardation [2]. These mutations result in altered dendrite pathology and abnormal fine dendrite structure. In this study we have used a mouse model (MeCP2 A140V "knock-in" mutant) expressing a human MeCP2 mutation linked to an X-linked mental retardation phenotype [3]. The major pathological findings in the A140V mouse include increased cell packing density and aberrant dendrite branching, similar to what is observed in human RTT patients.

Diffusion Tensor Imaging (DTI) is an MRI method that measures directional diffusion of water protons and how this diffusion is influenced by tissue structure [4,5]. In the gray matter, DTI parameters such as fractional anisotropy (FA) are influenced by both the large dendrite fibers perpendicular to the surface of the cortex and to a lesser extent the density of the fine lateral dendritic branches. The goal of this research is to use high-resolution DTI to quantify differences in FA in the somatosensory cortex of WT and MeCP2-A140V mutant mice.

Methods

Wild type (C56BL/6) and MeCP2-A140V mice (n= 5 per group) were imaged using a using a 7T small-animal scanner (Bruker BioSpin, Billerica, MA). T2-weighted images through the entire brain were acquired to visualize brain structures (RARE, TR=4000 ms, TE=12 ms, TEeff=60ms, RF=8, 192X192 matrix, 0.109X0.109X0.5 mm voxels, 30 slices). Diffusion data was collected along 12 diffusion directions using a diffusion-weighted Spin Echo sequence (TR=3500 ms, TE=18.5 ms, 170X170 matrix, 0.124X0.124X1.0 mm voxels, B=1000 s/mm^2). Following imaging, animals were sacrificed for histology. Scholl analysis on Golgi-Cox stained brain sections from both WT and MeCP2-A140V mice was performed to examine differences in dendritic branching.

Results

A significant increase (35%) in cortical FA (Fig. 1) was found in the MeCP2-A140V mice (MeCP2-A140V: 0.136±0.03 vs. WT: 0.101±0.01, $P < 0.05$). No difference was detected in white matter anisotropy (MeCP2-A140V: 0.528±0.21 vs. WT: 0.529±0.19). Scholl analysis of Golgi-Cox stained tissue (Fig. 2) reveals significant differences in the dendritic braching in both apical ($P<0.01$) and basal dendrites ($P<0.001$) in the somatosenory cortex.

Conclusion

In vivo DTI revealed significant increases in FA in the grey matter of the cortex of MeCP2-A140V mice. The differences in FA occur in the same area where there is abnormal dendritic structure, while there is no difference in FA in the white matter. These results indicate that DTI has the potential to be a valuable non-invasive tool for studying changes in dendritic structure in MeCP2-A140V mice and to evaluate therapies preclinically.

References

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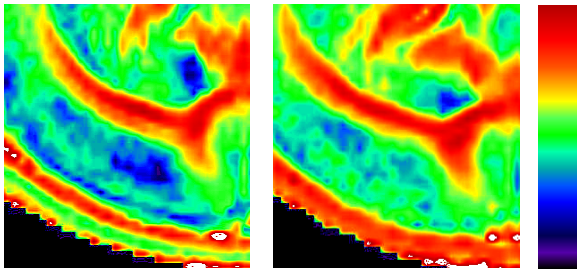
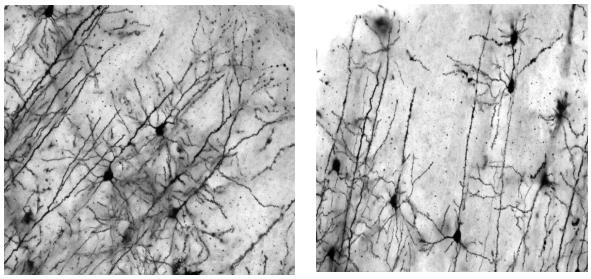


WT MeCP2-A140V

Fig. 1 Example FA maps of cortex of WT and MeCP2-A140V mice.



WT MeCP2-A140V

Fig. 2 Golgi-Cox stained cortical tissue show abnormal dendritic branching in the MeCP2-A140V mice compared to WT.