EVALUATION OF DEMYELINATION IN A NEW MYELIN BASIC PROTEIN MUTANT MOUSE USING IN VIVO MRI

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Target audience

This abstract is relevant to basic scientists with an interest in models of demyelination or using in vivo MRI to screen for white matter alterations in mice.

Introduction

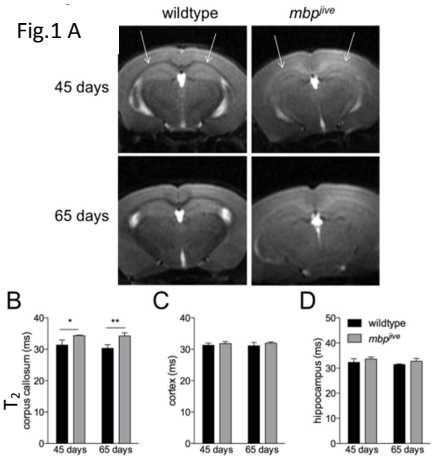
Myelin is essential for efficient signal transduction in the nervous system comprising of multiple proteins. The intricacies of the regulation of the formation of myelin, and its components, are not fully understood making mouse models an essential tool to enhance such knowledge. With this study we intended to characterize in vivo a novel myelin basic protein mutant (*mbp^{jive}*). We show that a fast diffusion tensor imaging (DTI) method is sufficient to characterize the loss of axonal integrity which is further supported by anatomical imaging.

Materials & Methods

- *Mice*: *Mbp^{jive}* mice arose as a spontaneous mutation in our C57BL/6 breeding colony, and were maintained by heterozygous breeding. For this imaging study we compared *Mbp^{jive}* mice with control C57BL/6 mice (both n=5)
- *MRI*: Mice were scanned at 35 days (*mbp^{jive} : 3;* C57BL/6: 2) and 70 days (*mbp^{jive} : 2;* C57BL/6: 3) old under isoflurane anesthesia. MR images were recorded on a 9.4 T Biospec small animal MR system (20 cm horizontal bore, Bruker Biospin, Ettlingen, Germany) using a 7 cm linearly polarized resonator for transmission and an actively-decoupled mouse brain surface coil for receiving (Rapid Biomedical, Rimpar, Germany). For T_2 relaxometry parameters were: repetition time (TR) 2.9 s, echo times (TE) from 12 to 120 ms. T_1w images were obtained using a 3D inversion prepared gradient echo sequence with parameters: TR 3.5 s, TE 3.3 ms, an inversion time of 1075 ms. Scan parameters for the DTI were: TR 1.0 s, TE 27.9 ms, 30 isotropically distributed diffusion directions, b = 2500 s/mm2, resol. 156x156x312 µm recorded in 20 min.
- *Processing*: Parametric images were calculated using home-written software in mevislab (Mevis Medical Solutions AG, Bremen, GE) and python (Pyhton software foundation). For DTI processing, first an Eddy current correction was applied using the FSL module [1] followed by an in-house

Results

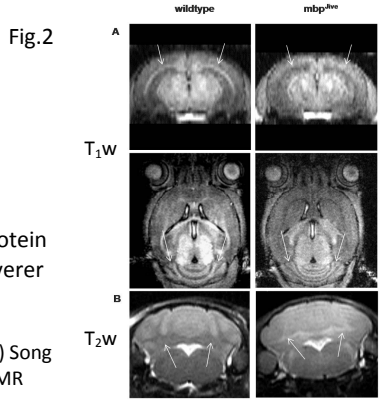
Analysis of the MRI data demonstrated that *mbp^{jive}* mice displayed a significant increase in the T_2 relaxation times and altered T_1 contrast for the corpus callosum, but not in the more prominent grey matter structures such as the cortex and hippocampus (fig 1a-d). Anatomical imaging also suggests alterations in the cerebellum (fig2). In vivo DTI further supported the white matter alterations through significant changes in fractional anisotropy and radial diffusivity (table 1: left cortex LC , right cortex RC and corpus callosum CC).



Discussion

The MRI signature based on the T_1 and T_2 contrast changes and the observed diffusion alterations correspond closely to what has been reported in Shiverer mice [3-5]. In particular the significantly increased radial diffusivity observed here has been associated with demyelination in the Shiverer mice therefore suggesting similar degradation in the *mbp^{jive}* mice. Importantly, this fast DTI protocol is accurately detects such alterations in axonal integrity *in vivo*, making this method interesting for the rapid validation of similar models.

table 1	FA			MD (mm2/s)			AD			RD		
	LC	RC	CC	LC	RC	CC	LC	RC	CC	LC	RC	CC
Wilde type d45	**0.126**	**0.118**	**0.378**	**6.4E-04**	**6.4E-04**	**6.2E-04**	**7.2E-04**	**7.1E-04**	**8.7E-04**	**6.0E-04**	**6.0E-04**	**4.9E-04**
sd	0.009	0.003	0.014	2.6E-05	2.2E-05	5.8E-06	3.7E-05	2.1E-05	5.6E-07	2.1E-05	2.2E-05	8.5E-06
mbp^{jive} d45	**0.131**	**0.147**	**0.325**	**6.7E-04**	**6.7E-04**	**6.9E-04**	**7.7E-04**	**7.7E-04**	**9.3E-04**	**6.3E-04**	**6.2E-04**	**5.7E-04**
sd	0.010	0.037	0.035	5.2E-05	4.2E-05	4.6E-05	6.6E-05	7.5E-05	3.6E-05	4.5E-05	2.6E-05	5.1E-05
Wilde type d65	**0.122**	**0.118**	**0.400**	**6.3E-04**	**6.2E-04**	**6.1E-04**	**7.1E-04**	**7.0E-04**	**8.7E-04**	**5.9E-04**	**5.8E-04**	**4.7E-04**
sd	0.011	0.006	0.019	1.2E-05	1.2E-05	5.0E-06	1.9E-05	1.7E-05	1.8E-05	1.1E-05	1.0E-05	9.9E-06
mbp^{jive} d65	**0.116**	**0.123**	**0.351**	**6.2E-04**	**6.2E-04**	**6.5E-04**	**6.9E-04**	**6.9E-04**	**9.0E-04**	**5.8E-04**	**5.8E-04**	**5.3E-04**
sd	0.011	0.006	0.002	2.0E-05	2.7E-05	1.2E-05	3.0E-05	2.6E-05	2.1E-05	1.5E-05	2.7E-05	7.4E-06
day 43 t-test	*0.594*	*0.316*	*0.104*	*0.376*	*0.332*	*0.111*	*0.401*	*0.293*	*0.127*	*0.360*	*0.458*	*0.106*
day 65 t-test	*0.596*	*0.495*	***0.046***	*0.702*	*0.822*	*0.091*	*0.671*	*0.902*	*0.312*	*0.738*	*0.784*	***0.007***



Conclusion

We show that with a 20 min in vivo DTI scan demyelination can be observed in this new myelin basic protein mutant and that axial and radial diffusivity changes closely resembles those previously reported for Shiverer mice.

Refs: (1) Jenkinson M et al. (2012) Neuroimage 62: 782-790. (2) Garyfallidis E et al. (2014) Front Neuroinform 8: 8. (3) Song SK et al. (2002) Neuroimage 17: 1429-1436 (4) Nair G, et al. (2005) Neuroimage 28: 165-174. (5) Ou X et al. (2009) NMR Biomed 22: 480-487.