Comparison between DTI, MWF, and frequency shift mapping in assessing white matter damage of spinal cord

Evan I-Wen Chen[1,2], Jie Liu[2], Vanessa Wiggermann[1], Andrew Yung[1], Alexander Rauscher[1,3], and Piotr Kozlowski[1,3]

[1]*MRI Research Center, Vancouver, BC, Canada,* [2]*International Collaboration On Repair Discoveries, Vancouver, BC, Canada,* [3]*Radiology, University of British Columbia, Vancouver, BC, Canada*

Introduction

Understanding disease pathology in white and gray matter (WM/GM) is a fundamental to revealing insight into mechanisms of degeneration and injury both in brain and spinal cord. Newer methods of probing tissue microstructure include myelin water fraction (MWF) and diffusion tensor imaging (DTI), and recent focus on bio-physical mechanisms that produce contrast in gradient echo phase imaging in CNS [1-3] show local tissue microstructure also affecting frequency shifts, leading to the possibility of also using frequency mapping as a quantitative measure of WM integrity. Our study compares frequency shift mapping, MWF, and DTI for quantitative characterization of WM tissue damage in rat spinal cords. We use the dorsal column transection (DC-Tx) axotomy model to produce secondary WM degeneration cranial/caudal to the tract, then image them *ex-vivo* at several weeks post injury. Histology of the same cords are used as gold standard to characterize the injury, for comparison with MRI.

Methods

Spinal cord injury, surgery, MGE imaging, frequency maps, and histology are detailed in [4]. Cords also scanned with MWF (CPMG, TE=6.7ms, TR=1500ms, 12 avg, 32 echoes, 70um x 70um x 1000um, 256x256) and DTI (TE=37ms, TR=1500ms, 16 avg, 6 dir, 70um x 70um x 1000um, 128x128, b-factor 0, 750 s/mm^2) at 7T (Bruker Biospec 70/30). Additional fluorescence immunohistology on cord tissue was performed with antibodies dMBP (for degenerated myelin content) and NF/TubIII (for axons) and normalized to WM to show area optical density, in accordance with [4]. Data analyzed for normality (Kolmogorov-Smirnov), correlations (Pearson), and pair-wise multiple comparison (Tukey-Kramer, Kruskal-Wallis) with Medcalc (Ostend, Belgium).

		RETROGRADE Degeneration (Proximal)			WALLERIAN Degeneration (Distal)		
		Healthy	3-WPI	8-WPI	Healthy	3-WPI	8-WPI
Myelin (Eriochrome)	FG	1.02 ± 0.05	1.13 ± 0.01 (**)	1.14 ± 0.06 (&&)	1.11 ± 0.04	1.19 ± 0.10	0.86 ± 0.03 (+++,&&&)
	CST	0.95 ± 0.06	1.04 ± 0.07 (*)	1.03 ± 0.04	0.90 ± 0.05	1.14 ± 0.07 (***)	0.85 ± 0.06 (+++)
Degenerated Myelin (dMBP)	FG	0.95 ± 0.08	0.97 ± 0.11	0.93 ± 0.07	1.02 ± 0.08	1.23 ± 0.10 (***)	1.73 ± 0.20 (+++,&&&)
	CST	1.10 ± 0.05	1.19 ± 0.03	1.28 ± 0.05 (+++,&&&)	1.02 ± 0.12	1.21 ± 0.10 (**)	1.25 ± 0.06 (&&&)
Axons (NF/TubIII)	FG	1.06 ± 0.05	0.86 ± 0.06 (***)	0.81 ± 0.07 (&&&)	1.10 ± 0.05	0.78 ± 0.09 (***)	0.74 ± 0.08 (&&&)
	CST	0.84 ± 0.04	0.75 ± 0.05 (*)	0.70 ± 0.06 (&&&)	0.86 ± 0.07	0.67 ± 0.06 (***)	0.73 ± 0.04 (&&&)
Frequency	FG	-1.60 ± 0.34	-4.97 ± 0.66 (***)	-4.81 ± 0.63 (&&&)	-1.26 ± 0.27	-1.46 ± 0.42	1.61 ± 0.38 (&&&)
	CST	-1.85 ± 0.21	-3.49 ± 0.30 (***)	-4.58 ± 0.38 (+++,&&&)	-2.45 ± 0.20	-3.70 ± 0.51 (*)	-0.88 ± 0.38 (+,&&&)
MWF	FG	0.39 ± 0.05	0.39 ± 0.02	0.37 ± 0.03	0.42 ± 0.03	0.33 ± 0.02 (***)	0.19 ± 0.02 (+++,&&&)
	CST	0.34 ± 0.02	0.34 ± 0.06	0.35 ± 0.05 (&)	0.27 ± 0.03	0.44 ± 0.06 (***)	0.26 ± 0.04 (+++)
D_Long	FG	1.01 ± 0.07	0.97 ± 0.06	0.95 ± 0.06	1.02 ± 0.07	0.64 ± 0.01 (***)	0.78 ± 0.05 (+++,&&&)
	CST	0.95 ± 0.10	0.89 ± 0.06	0.93 ± 0.06	0.98 ± 0.10	0.71 ± 0.13 (***)	0.79 ± 0.05 (+++,&&&)
D_Trans	FG	0.02 ± 0.06	0.13 ± 0.05 (***)	0.16 ± 0.04 (&&&)	0.09 ± 0.04	0.32 ± 0.03 (***)	0.36 ± 0.03 (&&&)
	CST	0.09 ± 0.06	0.09 ± 0.03	0.12 ± 0.04	0.02 ± 0.06	0.13 ± 0.07 (**)	0.24 ± 0.03 (+++,&&&)

Table 1: Histology and MRI measures of degeneration (retrograde, Wallerian) tracked 3- and 8-weeks post injury (WPI). Histology measures normalized to healthy WM. Frequency in 10^{-3} ppm and DTI in 10^3mm^2/sec. Significant changes from Healthy to 3-WPI (*), 3-WPI to 8-WPI (+), and Healthy to 8-WPI (&). Indicators in single (*), double (**), and triplet (***) for $p < 0.05$, $p < 0.01$, and $p < 0.005$, respectively.

RETROGRADE Degeneration

		Healthy to 3-WPI	3-WPI to 8-WPI	Healthy to 8-WPI
F. Gracilis (Caudal)	Histology	Myelin (↑) Axons (↓)	No Change	Myelin (↑) Axons (↓)
	MRI	Frequency (↓) D_trans (↑)	No Change	Frequency (↓) D_trans (↑)
CST (Cranial)	Histology	Myelin (↑) Axons (↓)	degen-MBP (↑)	degen-MBP (↑) Axons (↓)
	MRI	Frequency (↓)	Frequency (↓)	Frequency (↓) MWF (↑)

WALLERIAN Degeneration

		Healthy to 3-WPI	3-WPI to 8-WPI	Healthy to 8-WPI
F. Gracilis (Cranial)	Histology	degen-MBP (↑) Axons (↓)	Myelin (↓) degen-MBP (↑)	Myelin (↓) degen-MBP (↑) Axons (↓)
	MRI	MWF (↓) D_long (↓) D_trans (↑)	↑ Frequency (↑) ↓ MWF (↓) ↑ D_long (↑)	Frequency (↑) MWF (↓) D_long (↓) D_trans (↑)
CST (Caudal)	Histology	Myelin (↑) degen-MBP (↑) Axons (↓)	Myelin (↓)	degen-MBP (↑) Axons (↓)
	MRI	Frequency (↓) MWF (↑) D_long (↓) D_trans (↑)	Frequency (↑) MWF (↓) D_long (↑) D_trans (↑)	Frequency (↑) D_long (↓) D_trans (↑)

Table 2: Comparison of significant changes MRI and histology parameters across time-points from healthy to 3- and 8-wpi. Arrows show direction of change

Results and Discussion

We assessed two DC tracts: the fasciculus gracilis (FG, ascending tract) and corticospinal (CST, descending) tract. Previous studies [4-5] show two types of secondary injury +/-5mm away from the injury site with closely matching pathology. Retrograde degeneration occurs proximally (in cranial FG, caudal CST), and Wallerian degeneration occurs distally (in Caudal FG, cranial CST). Averaged data showing values for all parameters at each time point [Table 1] indicate where and when most significant changes occur post-injury. In general, retrograde degeneration is a milder injury, with less severe changes than Wallerian degeneration. Each MRI parameter is evaluated against histologically to determine the most accurate for assessing pathology. [Table 2] shows data grouped by tract, listing parameters that change significantly between time-points (each time-point is a "case"). MWF shows increases during myelin damage (CST, retrograde 8-WPI, Wallerian 3-WPI) and large decreases with more myelin debris and debris removal (CST/FG, Wallerian) consistent with the literature [5-6]. However, MWF is limited to tracking myelin pathology and cannot provide a larger assessment of injury, while having less sensitivity than DTI and frequency shift mapping. DTI tracks axonal and myelin integrity with decreasing D_long and increasing D_trans (respectively) across most cases, showing clear signs of full neuronal degeneration by 8-wpi. Frequency shift mapping is predicted to reveal changes due to deviations from the anisotropic cylindrical structure of bundled DC fibers, reporting a net shift from the strongest contributing factor [3,7]. However, as a combined measure of both axonal and myelin structure, frequency shift mapping does not reveal the proportional contribution from either factor. In retrograde degeneration, decreased frequency shift with relatively minor MWF decrease suggest axonal debris as a primary factor. Wallerian degeneration, as a relatively faster mode of degeneration, completely destroys axons by 3-wpi. Subsequent injury is mostly in myelin, as reflected in the frequency shift increases (healthy to 8-wpi and 3- to 8-wpi). Sensitivity-wise, we observe that given a change in pathology (histology parameters), frequency mapping changes most frequency (10 of 11 cases), followed by diffusion (8 cases), and MWF being least sensitive (6 cases). One advantage of using frequency is evident in retrograde degeneration, as it is the only method sensitive to histology changes in all cases.

Conclusion

In this study, white matter degeneration from the DC-Tx injury was characterized with histology and compared to multiple MRI techniques. Similar to established methods of assessing WM (MWF and DTI), frequency shift mapping expresses significant changes relative to changes seen in histology, which suggests good sensitivity. Additionally, it has the advantage of higher spatial resolution (also in 3D) with relatively higher SNR, more sensitivity to pathology, and lower scan times compared to DTI and MWF. If limited to one method, our results show frequency shift mapping offers a sensitive method of detecting tissue change, but is difficult to interpret as specific changes in either axonal or myelin integrity. Rather, DTI can provide additional structural information that may help in interpreting frequency results, and thus as a combined method, frequency shift mapping and DTI together offers a more complete (though not total) picture of injury, better separating axonal and myelin degeneration while remaining easy to implement clinically. This study does not preclude the possibility of other MRI methods in WM assessment. For instance, magnetization transfer (MT) has also seen increasing use for quantifying tissue damage, and would be interesting to compare in a further expanded study.

References

[1] Rauscher, et al. 2005. AJNR. (26):736-42 [2] He et al. 2009. PNAS. (106) 13558-563 [3] Yablonskiy, et al. 2012. PNAS. (109):14212-7 [4] Chen, et al. 2013. Proc. ISMRM 21 (Abstract #0347) [5] Kozlowski, et al. 2008. J Neurotrauma. (6):653-76 [6] Kozlowski, et al. 2014. MRM. 32(3):250-8 [7] Denk, et al. 2011. NMR Biomed. 24(3):246-52

Acknowledgements: This work was supported by the Canadian Institutes of Health Research (CIHR) and the Natural Sciences and Engineering Research Council of Canada (NSERC)