Available online freely at www.isisn.org

Bioscience Research

Print ISSN: 1811-9506 Online ISSN: 2218-3973

Journal by Innovative Scientific Information & Services Network

RESEARCH ARTICLE BIOSCIENCE RESEARCH, 2023, 20(2):623-630. **OPEN ACCESS**

The role of diffusion magnetic resonance imaging in diagnosing brain Multiple Sclerosis at Taif hospitals following the recent consensus guidelines

Ahmad Joman Alghamdi *

Radiological Sciences Department, College of Applied Medical Sciences, Taif University, Taif, 21944, **Saudi Arabia**

***Correspondence:** a.joman@tu.edu.sa **Received:16-04-2023, Revised: 20-06-2023, Accepted: 22-06-2023 e-Published: 26-06-2023**

Background: Several consensus recommendations have been published on the use of magnetic resonance imaging (MRI) for diagnosing, prognosing, and monitoring patients with multiple sclerosis (MS). They provided standardized protocols and guidance for when and how to use MRI. Objective: this study aims to investigate the diffusion weighted imaging (DWI) parameters and the diffusion data processing modalities used to diagnose MS in Taif city hospitals. Methods: data were collected from the radiology departments of the Ministry of Health hospitals in Taif city (King Faisal Medical Complex and King Abdul-Aziz Specialist Hospital). The 2021 MAGNIMS-CMSC-NAIMS consensus recommendations on the use of MRI in patients with MS was used as a guidance for this paper. Results: Both hospitals do not follow the 2021 MAGNIMS-CMSC-NAIMS consensus recommendations on when to acquire DWI images. Instead, they always acquire DWI for every MS patient. However, they met the recommendation of using magnetic field strength larger than 1.5T.The 2021 MAGNIMS-CMSC-NAIMS consensus recommendations did not specify DWI parameters. Thus, recent MS clinical studies were investigated to identify the importance of acquiring proper diffusion weighted (DW) images considering the acquisition time. Conclusion: A combination of different DWIpost-processing modalities cans helpunderstanding MS pathological background. Moreover, using flexible DWI protocol allows for processing diffusion data with multiple modalities to investigate the disease microstructural changes and the treatment efficacy.

Keywords: multiple sclerosis; magnetic resonance imaging; diffusion weighted imaging; diffusion tensor imaging; diffusion kurtosis imaging; neurite orientation dispersion and density imaging.

INTRODUCTION

Multiple Sclerosis (MS)is an inflammatory demyelination disease that attacks the central nervous system and causes myelin loss leading to sensory or/and motor malfunctions. MS has increased since 2008 from 2.1 million to 2.8 million in 2020 worldwide and the mean age of diagnosis now is 32 years (Walton et al. 2020). The recent estimation from Saudi Arabia is 40.4 cases per 100,000 population, and 61.95 cases per 100,000 population of Saudi citizens (Saeedi et al. 2023).

Magnetic resonance imaging (MRI) plays an important role in diagnosing MS. Clinical evaluations underestimate the disease activity when compared with MR imaging. Moreover, MRI technique has higher sensitivity to myelin changes than other imaging techniques(Simon et al. 2006; Traboulsee et al. 2016a). On the other hand, monitoring MS progression as well as the therapy response has been hindered by inconsistent protocols and their imaging quality (Traboulsee et al. 2016a). Thus, it was essential to standardise the imaging protocol for a proper disease investigation (Simon et al. 2006; Traboulsee et al. 2016a).

McDonald Criteria provides the most updated guidance for clinicians and researchers regarding the clinical evaluation and imaging techniques that may help in diagnosing MS rapidly. MS disease diagnosis has been relied heavily on McDonald criteria since it was published by McDonald et al. (2001) in 2001. This criteria went through different revisions in 2005 (Chris H. Polman et al. 2005), 2010 (C. H. Polman et al. 2011), and lastly 2017 (Thompson et al. 2018). Since Macdonald criteria was published, MRI was the preferred diagnostic tool for MS assessment and treatment monitoring (M. Filippi et al. 2016; Simon et al. 2006; Traboulsee et al. 2016a).

The 2015 Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) (Rovira et al. 2015; Mike P. Wattjes et al. 2015) and 2016 Consortium of Multiple Sclerosis Centres (CMSC)(Traboulsee et al. 2016a) guidelines on MRI usage in diagnosing and monitoring MS have improved the knowledge about the importance of MRI in the routine clinical practice. Their contribution helpedin McDonald diagnostic criteria 2017 revision, renewing the intravenous gadolinium-based contrast agents safety concerns, as well as highlighting the importance of acquiring spinal cord MRI for predicting, diagnosing, and

monitoring patients with MS(M. P. Wattjes et al. 2021). These information and other new developments in MRI field regarding MS encouraged MAGNIMS, CMSC, and North American Imaging in Multiple Sclerosis Cooperative (NAIMS) to publish consensus recommendations on the use of MRI for diagnosis, prognosis, and monitoring patients with MS, guiding for a standardising the imaging protocols and the symptoms for when and how to use MRI, motivating the national and international societies in founding similar guidance (M. P. Wattjes et al. 2021). The guidelines suggested the acquisition of axial 3D (1mm isotropic; recommended) or 2D (≤ 3mm without gaps) images with an in-plane resolution of ≤ 1mm x 1mm for the whole brain. It is also recommended to include as much as possible of the cervical spinal cord using not less than 1.5T MR scanner (preferably 3 T) for the imaging protocols in table 1. The guidelines have highlighted the importance of acquiringdiffusion weighted imaging (DWI)protocol for MS patients as: I) optional when diagnosing MS for the first time(M. P. Wattjes et al. 2021); II) optional when following-up the disease activity and/or for differential diagnosis(M. P. Wattjes et al. 2021);and III) recommended core for safety monitoring the effectiveness of disease modifying treatment(Bagnato & Wallin, 2022; M. P. Wattjes et al. 2021).

DWI was firstly introduced in evaluating MS patients in 1992 (Larsson, Thomsen, Frederiksen, Stubgaard, & Henriksen, 1992). Larsson et al. (1992) study found that water diffusion in MS plaques is higher than normal tissue as well as in MS acute plaques than in the chronic phase. This increase in diffusion caused by an increase of the extracellular space due to demyelination. Science then, the application of DWI was increased with various advanced modalities to investigate MS such as diffusion tensor imaging (DTI), diffusion kurtosis imaging (DKI), q-space imaging (QSI), composite hindered and restricted model of diffusion (CHARMED), and neurite orientation dispersion and density imaging (NODDI). Each modality has its own pros and cons; however, combining more than one may contribute to deliver more details about the disease and emphasize the complementary information. DTI sensitivity in detecting abnormalities caused by MS is high in focal lesions, normal appearing white matter (NAWM) and gray matter (GM). However, fractional anisotropy (FA; one of DTI-derived metrics) lack specificity in differentiating the microstructure sub-compartments of white matter (WM). In consideration of MS, similar effect on DTI metrics will be detected when either axonal loss or demyelination was present and thus cannot be distinguished. Also, the apparent diffusion coefficient (ADC) derived-metric from tensor modelling of DTI is a sensitive but not specific metric when evaluating an environment of highly heterogeneous tumour (Wen et al. 2015). These issues and other limitations of DTI introduced several advanced diffusion imaging methods to overcome them. DKI can extract the deviation of water diffusion displacement profile from MRI signal decay of DTI exponential model using excess kurtosis (a dimensionless metric) (Jensen, Helpern, Ramani, Lu, & Kaczynski, 2005). The mean kurtosis (one of DKI indices) has been found to be affected in MS patients compared to healthy controls (Guglielmetti et al. 2016). Additionally, white matter tract integrity (WMTI; can be extracted from DKI) provides details about the axonal integrity and extra axonal space enabling to differentiate patients with mild cognitive deterioration (E. Fieremans et al. 2013; Els Fieremans, Jensen, & Helpern, 2011), and improve detecting morphological changes in WM of lesions with chronic demyelination (Falangola et al. 2014). Also, a significant correlation was found between DKI metrics and the expanded disability status scale (EDSS) (De Kouchkovsky et al. 2016). Moreover, WMTI have showed its sensitivity in monitoring changes in myelination during brain development (Jelescu et al. 2015) as well as showing correlation with N-acetyl-aspartate levels with mild brain trauma (Grossman et al. 2015).QSI, a non-parametric analysis, has a model-free index known as P_0 (zero displacement probability) that calculates the probability of water molecules with no net diffusion within the diffusion time. This index showed a decrease in WM myelin defects and in NAWM in MS patients, which suggests a myelin damage or axons loss (Mustafi et al. 2019; Wu et al. 2011). CHARMED Model can separate the signal decay coming from water diffusion molecule either from intracellular or extracellular space in DWI and then distinguish the effect of axonal loss from those due to demyelination (Assaf & Basser, 2005). It creates maps of the restricted water fraction (FR), which represents the axonal density. FR showed an increased specificity and sensitivity to microstructural changes in early stages of MS in lesions and NAWM (S. De Santis et al. 2017). To such a degree, besides the restricted water fraction (known as intracellular fraction (IC) in NOODI), NODDI has the ability to quantify fibre orientation dispersion (ODI) index. Recent studies reported an increase in sensitivity and specificity in differentiating MS patients from healthy controls when conducting an investigation into WM (Granberg et al. 2017; Schneider et al. 2017), GM (Granberg et al. 2017) and spinal cord (By, Xu, Box, Bagnato, & Smith, 2017).

The adherence to the guidelines of MS imaging in Taif hospitals as described by Traboulsee and his colleagues has been covered previously by Alamri (2020) in 2020.

This paper aims to investigate when DWI protocolis applied for brain MS patients' inTaif hospitals and compare it to2021 MAGNIMS-CMSC-NAIMS consensus recommendations. Moreover, investigating the used parameters of DWI protocol and compare it to recent MS clinical studies.

Table 1: The recommended brain protocols by 2021 MAGNIMS-CMSC-NAIMS international consensus on the use of MRI in patients with MS.

Brain imaging protocol	Diagnosis	Follow-up	Safety monitoring
Axial T2	Recommended core	recommended core or optional if 3D Fluid attenuated inversion recovery (FLAIR) with sagittal/axial reconstructions are available	recommended core or optional if 3D FLAIR with sagittal/axia l reconstruction s are available
Sagittal and axia l (or 3D) FLAIR	Recommended core	Recommended core	Recommended core
Axial (or 3D) T1 Post-gadolinium	Recommended core	Optional	Optional
DWI	Optional	Optional for differentia l diagnosis	Recommended core
Double inversion recovery (DIR) or phase sensitive inversion recovery (PSIR)	Optional	Optional	Optional
High-resolution 3D T1 (for brain volume assessment)	Optional	Optional	Not required
Susceptibility-weighted imaging	Optional	Not required	Not required

MATERIALS AND METHODS

DWI parameters were collected from MRI scanners at the radiology department of the main Ministry of Health hospitals in Taif city, which are King Faisal Medical Complex (KFMC) and King Abdul-Aziz Specialist Hospital (KASH) (Table. 2). Ethical approval was received from the Institutional Review Board of the Ministry of Health in the Kingdom of Saudi Arabia for conducting this research on Taif hospitals.

Table 2: DWI parameters in Taif hospitals.

	KFMC		**KASH**	
Magnetic field strength (Tesla (T))	1.5 T Optima MR450w GE Healthcare	3 T Siemens Magneton Skyra	1.5 T Optima MR450w GE Healthcare	1.5 T Optima MR450w GE Healthcare
Slice thickness (mm)	5	4	4	5
Slice orientation	Oblique Axial	Anterior-posterior transverse	Oblique Axial	Oblique Axial
Used b-value (s/mm^2)	0 and 1000	0 and 1000	0, 500, and 1000	0, 500, and 1000
Number of diffusion directions	3	3	3	3
Number of slices	28	27	30	23
Pixel size (mm)		0.7 x 0.7	1.8 x 1.2	1 x 1
Spacing gap (mm)	0.5 (10%)	1.2 (30%)	0.4 (10%)	1 (20%)
TR (ms)	5450	5640	8667	4911
TE (ms)	74.4	64	70	71.5
NEX	1		1	1
When DWI is acquired?	With every request for suspected or diseased MS patients.			
Head coil	GEM head and neck unit (HNU)	20-channel Head/Neck coil	GEM head and neck unit (HNU)	GEM head and neck unit (HNU)
Total scan time (Minutes: Seconds)	00:44	02:06	01:35	1:38

RESULTS AND DISCUSSION

Standardising MRI MS brain protocols is an essential step towards acquiring better images to interpret ate the disease indications accurately. This study aimed to investigate DWI parameters for MS at KFMC and KASH (shown in Table 2). Both hospitals in Taif city do not follow the 2021 MAGNIMS-CMSC-NAIMS international consensus recommendations on when to acquire DWI images. Instead, they always acquire DWI for every MRI request for either suspected or diseased MS patient. This follows the argument raised by Veterans Health Administration radiologists that DWI protocol should always be acquired for brain MS patients (Bagnato & Wallin, 2022), which is in line with the revised recommendations of the consortium of MS centerstask force for a standardized MRI Protocol and clinical guidelines for the diagnosis and follow-up of MS published in 2016 by Traboulsee et al. (2016b). This is because it is important to detect changes in ADC, which was reported to be increased in MS lesions (Castriota-Scanderbeg et al. 2002; Huisman, Sorensen, Hergan, Gonzalez, &Schaefer, 2003), reduced in acute phase of MS due to the cytotoxic oedema that would be converted, in the subsequent days, to either normal or increased ADC signal along with the inflammatory vasogenic oedematous(Bugnicourt et al. 2010; Castriota-Scanderbeg et al. 2002; Eisele et al. 2012; Pagani et al. 2007; Rosso et al. 2006). Quantitative in-vivo MRI methods (such as DWI, spectroscopy, magnetization transfer, and relaxation times) have proven a presence of abnormalities in NAWM from clinical onset of MS and becomes clearer in MRI with disease progression and, later, leads to increase of lesions number and disability score (Massimo Filippi et al. 2012).

On the other hand, a Taif city hospital follows the 2021 MAGNIMS-CMSC-NAIMS international consensus recommendations in using magnetic field strength with more than 1.5 T in diagnosing MS. A 3 T MRI scanner is usually considered the best option in diagnosing MS, whereas a 10-minute multi-shell DWI at ultra-high magnetic field (7 T scanner) has shown similar interpretation in MS to those at 3 T (Silvia De Santis et al. 2019).

On the contrary, the 2021 MAGNIMS-CMSC-NAIMS international consensus recommendations did not specify DWI parameters. It only highlighted the slice thickness of the two-dimensional DWI ,which should be less or equal to 5 mm with a slice gap not exceeding 10-30%. Thus, recent MS clinical studies (Table 3) were investigated in order to identify the importance of acquiring proper DWI images taking into account the acquisition time.

Our data revealed that only three directions for all DWI protocols are acquired for both hospitals. This is for the purpose of calculating the ADC index to check for any alterations caused by edema that resulted from the primary inflammations of MS(Davoudi et al. 2016).Moreover, KFMC DWI protocols have only one b-value (1000 s/mm^2) while KASH acquires two (500 and 1000 s/mm^2). Acquiring more directions with large numberof b-values will help in providing further knowledge about MS pathology not only for calculating ADC, but also for analysing DWI data with other methods.

Several studies (De Kouchkovsky et al. 2016; Li et al. 2018; Stulík et al. 2022) has analysed the DWI data using the tract-based spatial statistics (TBSS), which is considered as a hypothesis-free and user-independent voxel-wise analysis to implement multi-subject comparisons. They reported widespread differences in TBSS analysis reflected by DTI and DKI parameters for the NAWM skeleton of MS patients compared to healthy control. Moreover, a more sophisticated micro structural models (such as DKI, CHARMED and NODDI) describes the tissue changes in both lesions and NAWM in MS better than DTI metrics. They are even more sensitive in detecting differences in relatively small cohort analysis for the clinical routine (Silvia De Santis et al. 2019). In General, the changes in MS compared to healthy controls was reported as: a) in DTI, an increase in the mean diffusivity (MD) and radial diffusivity (RD) (Qian et al. 2016) and a decrease FA in lesions and NAWM (Mustafi et al. 2019; Qian et al. 2016); b) in DKI, metrics showed a reduction in lesions and NAWM (Bester et al. 2015; Silvia De Santis et al. 2019; Qian et al. 2016) and reduced mean kurtosis (MK) in the normal appearing GM (Bester et al. 2015; Silvia De Santis et al. 2019); c) in NODDI, a decrease in IC in lesions and NAWM (Caverzasi et al. 2016; Collorone et al. 2021; Granberg et al. 2017; Hagiwara et al. 2017; Hagiwara et al. 2019; Lakhani, Schilling, Xu, & Bagnato, 2020; Mustafi et al. 2019; Sacco et al. 2020; Spanò et al. 2018), and a decrease in ODI in lesion and increase in NAWM (Schneider et al. 2017); d) in CHARMED, a decrease in FR in lesions and NAWM; and e) in QSI, a decrease in tissue restriction (P_0) (Mustafi et al. 2019).

Fujiyoshi et al. (2016) has investigated the sensitivity of myelin map obtained from QSI for a 35-year-old female patient with relapsing remitting MS (RRMS) using 3T scanner. She was complaining from weakness and tactile hypoesthesia in her left arm due to acute relapses and scored with 2/10 in EDSS. MRI revealed a hyperintense lesion in T2 weighted images (T2WI) with gadolinium in the left side of the cervical spinal cord (C4/C5 level). At the same lesion site, a major myelin signal loss was detected in the myelin map. Ten weeks after an intravenous methylprednisolone therapy (IVMP), the patient was scored with normal EDSS (0/10), and the myelin map showed a significant recovery of myelin signal in the lesion location. In comparison, the lesion continued to exist with a hyper intense signal on T2WI throughout the IVMP time

Table 3. MRI clinical studies utilized DWI in MS.

	(Li et al., 2018)	**(De Kouchkovsky et al., 2016)**	**(Silvia De Santis et al., 2019)**		**(Qian et al., 2016)**	**(Bester et al., 2015)**	**(Stulík et al., 2022)**	**(Mustafi et al., 2019)**	**(Fujiyoshi et al., 2016)**
Magnetic field strength (Tesla (T))	3 T Discovery MR750 scanner GE Healthcare	3 T Siemens Tim Trio	3 T Siemens Prisma Fit		3 T Philips Achieva	3 T Siemens Tim Trio	1.5 T Philips Achieva OR 1.5 T Philips Ingenia	3 T Philips Achieva	3 T Discovery MR750 scanner GE Healthcare
Slice thickness (mm)	4	2.7	1.5		3	2.7	2	3	5
Slice orientation	Axial	Axial	n/a		Axial	Axial	Axial	Axial	n/a
Used b-value (s/mm^2)	0, 1250 and 2500 for DKI, 0 and 1250 for DTI	0, 1000 and 2000	0, 700 and 2000	0, 750 – 6000	0, 1000 and 2000	0, 1000 and 2000	0 and 1000	0, 250, 1000, 2250, 4000 and 6250	0 – 10,000 in 9 steps for myelin imaging, 0 and 1066 for DTI
Number of diffusion directions	25	11 directions for b-value of 0 images, and 30 directions for b-values 1000 and 2000	6 directions for b-value of zero, 27 directions for b-value of 700, and 45 directions for b-value of 2000	12 directions for b-value of zero and, 106 directions distributed in eight shells of b-values from 750 to 6000	30 for each b-value	4 directions for b-value of 0 images, and 32 directions for b-values 1000 and 2000	32 for each b-value	The diffusion directions were 1, 6, 21, 24, 30 and 61 for b-values of 0, 250, 1000, 2250, 4000 and 6250; respectively	12
Number of slices	35	28	n/a		44	28	n/a	40	n/a
Pixel size (mm)	1 x 1	2.7 x 2.7	1.5 x 1.5		2.55 x 2.55	2.7 x 2.7	2 x 2	2 x 2	1 x 1
Spacing gap (mm)	No gap	n/a	n/a		No gap	n/a	n/a	n/a	n/a
TR (ms)	4700	3700	4873	6000	3700	2000	2100	3590	5000
TE (ms)	102	96	68	94	96	69	62	114.24	124
NEX	n/a	2	n/a		2	2	n/a	n/a	n/a
Head coil	8-channel phase array head coil	12-channel head coil	n/a		8-channel SENSE head coil	8-channel phase array head coil	16-channel head and neck coil	8-channel head coil	32-channel
Post processing	DKI and DTI	DKI	DTI, DKI, CHARMED and NODDI		DKI	DKI and DTI	DKI and DTI	DTI, NODDI and QSI	QSI and DTI
Total scan time (Minutes: Seconds)	08:42	n/a	08:00	12:00	07:58	19:39	n/a	24:00	≈ 09:00

.

CONCLUSION

In summary, MS changes can be detected using DWI. A combination of different diffusion imaging modalities might provide more knowledge in diagnosing MS as well as helping in clarifying the pathological background. Moreover, using flexible diffusion imaging protocols that allow for multiple modalities of diffusion data processing is essential for further investigation of the disease micro structural changes and the treatment efficacy.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

ACKNOWLEDGEMENT

I would like to thank all the radiology staff at KFMC and KASH for their assistance in providing all the necessary information during the period of collecting the data for this study.

REFERENCES

Alamri, S. (2020). Adherence to MRI Protocol Consensus Guidelines in Multiple Sclerosis Patients at Taif Hospitals. *International Journal of Medical Imaging, 8*(4), 102-105. doi:10.11648/j.ijmi.20200804.16

Assaf, Y., & Basser, P. J. (2005). Composite hindered and restricted model of diffusion (CHARMED) MR imaging of the human brain. *Neuroimage, 27*(1), 48-58. doi:http://dx.doi.org/10.1016/j.neuroimage.2005.03.042

Bagnato, F., & Wallin, M. (2022). Harmonizing Magnetic Resonance Imaging Protocols for Veterans With Multiple Sclerosis. *Fed Pract, 39*(Suppl 1), S10-s13. doi:10.12788/fp.0251

Bester, M., Jensen, J. H., Babb, J. S., Tabesh, A., Miles, L., Herbert, J., . . . Inglese, M. (2015). Non-Gaussian diffusion MRI of gray matter is associated with cognitive impairment in multiple sclerosis. *Mult Scler, 21*(7), 935-944. doi:10.1177/1352458514556295

Bugnicourt, J. M., Garcia, P. Y., Monet, P., Bonnaire, B., Al Khedr, A., & Godefroy, O. (2010). Teaching NeuroImages: marked reduced apparent diffusion coefficient in acute multiple sclerosis lesion. *Neurology, 74*(20), e87. doi:10.1212/WNL.0b013e3181df09f7

By, S., Xu, J., Box, B. A., Bagnato, F. R., & Smith, S. A. (2017). Application and evaluation of NODDI in the cervical spinal cord of multiple sclerosis patients. *NeuroImage : Clinical, 15*, 333-342. doi:10.1016/j.nicl.2017.05.010

Castriota-Scanderbeg, A., Sabatini, U., Fasano, F., Floris, R., Fraracci, L., Mario, M. D., . . . Caltagirone, C. (2002). Diffusion of water in large demyelinating lesions: a follow-up study. *Neuroradiology, 44*(9), 764-767. doi:10.1007/s00234-002-0806-y

Caverzasi, E., Papinutto, N., Castellano, A., Zhu, A. H., Scifo, P., Riva, M., . . . Henry, R. G. (2016). Neurite Orientation Dispersion and Density Imaging Color Maps to Characterize Brain Diffusion in Neurologic Disorders. *J Neuroimaging, 26*(5), 494-498. doi:10.1111/jon.12359

Collorone, S., Prados, F., Kanber, B., Cawley, N. M., Tur, C., Grussu, F., . . . Toosy, A. T. (2021). Brain microstructural and metabolic alterations detected in vivo at onset of the first demyelinating event. *Brain, 144*(5), 1409-1421. doi:10.1093/brain/awab043

Davoudi, Y., Foroughipour, M., Torabi, R., Layegh, P., Matin, N., & Shoeibi, A. (2016). Diffusion Weighted Imaging in Acute Attacks of Multiple Sclerosis. *Iran J Radiol, 13*(2), e21740. doi:10.5812/iranjradiol.21740

De Kouchkovsky, I., Fieremans, E., Fleysher, L., Herbert, J., Grossman, R. I., & Inglese, M. (2016). Quantification of normal-appearing white matter tract integrity in multiple sclerosis: a diffusion kurtosis imaging study. *Journal of Neurology, 263*(6), 1146-1155. doi:10.1007/s00415-016-8118-z

De Santis, S., Bastiani, M., Droby, A., Kolber, P., Zipp, F., Pracht, E., . . . Roebroeck, A. (2019). Characterizing Microstructural Tissue Properties in Multiple Sclerosis with Diffusion MRI at 7 T and 3 T: The Impact of the Experimental Design. *Neuroscience, 403*, 17-26. doi:https://doi.org/10.1016/j.neuroscience.2018.03.048

De Santis, S., Granberg, T., Ouellette, R., Treaba, C. A., Qiuyun, F., Herranz, E., . . . Toschi, N. (2017). Early axonal damage in normal appearing white matter in multiple sclerosis: Novel insights from multi-shell diffusion MRI. *Annu Int Conf IEEE Eng Med Biol Soc, 2017*, 3024-3027. doi:10.1109/embc.2017.8037494

Eisele, P., Szabo, K., Griebe, M., Rossmanith, C., Förster, A., Hennerici, M., & Gass, A. (2012). Reduced diffusion in a subset of acute MS lesions: a serial multiparametric MRI study. *AJNR Am J Neuroradiol, 33*(7), 1369-1373. doi:10.3174/ajnr.A2975

Falangola, M. F., Guilfoyle, D. N., Tabesh, A., Hui, E. S., Nie, X., Jensen, J. H., . . . Helpern, J. A. (2014). Histological correlation of diffusional kurtosis and white matter modeling metrics in cuprizone-induced corpus callosum demyelination. *NMR in Biomedicine,*

27(8), 948-957. doi:https://doi.org/10.1002/nbm.3140

Fieremans, E., Benitez, A., Jensen, J. H., Falangola, M. F., Tabesh, A., Deardorff, R. L., . . . Helpern, J. A. (2013). Novel white matter tract integrity metrics sensitive to Alzheimer disease progression. *AJNR Am J Neuroradiol, 34*(11), 2105-2112. doi:10.3174/ajnr.A3553

Fieremans, E., Jensen, J. H., & Helpern, J. A. (2011). White matter characterization with diffusional kurtosis imaging. *Neuroimage, 58*(1), 177-188. doi:https://doi.org/10.1016/j.neuroimage.2011.06.006

Filippi, M., Rocca, M. A., Barkhof, F., Brück, W., Chen, J. T., Comi, G., . . . Lassmann, H. (2012). Association between pathological and MRI findings in multiple sclerosis. *The Lancet Neurology, 11*(4), 349-360. doi:http://dx.doi.org/10.1016/S1474-4422(12)70003-0

Filippi, M., Rocca, M. A., Ciccarelli, O., De Stefano, N., Evangelou, N., Kappos, L., . . . Barkhof, F. (2016). MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. *Lancet Neurol, 15*(3), 292-303. doi:10.1016/s1474-4422(15)00393-2

Fujiyoshi, K., Hikishima, K., Nakahara, J., Tsuji, O., Hata, J., Konomi, T., . . . Okano, H. (2016). Application of q-Space Diffusion MRI for the Visualization of White Matter. *The Journal of Neuroscience, 36*(9), 2796. doi:10.1523/JNEUROSCI.1770-15.2016

Granberg, T., Fan, Q., Treaba, C. A., Ouellette, R., Herranz, E., Mangeat, G., . . . Mainero, C. (2017). In vivo characterization of cortical and white matter neuroaxonal pathology in early multiple sclerosis. *Brain, 140*(11), 2912-2926. doi:10.1093/brain/awx247

Grossman, E. J., Kirov, I. I., Gonen, O., Novikov, D. S., Davitz, M. S., Lui, Y. W., . . . Fieremans, E. (2015). N-acetyl-aspartate levels correlate with intra-axonal compartment parameters from diffusion MRI. *Neuroimage, 118*, 334-343. doi:https://doi.org/10.1016/j.neuroimage.2015.05.061

Guglielmetti, C., Veraart, J., Roelant, E., Mai, Z., Daans, J., Van Audekerke, J., . . . Verhoye, M. (2016). Diffusion kurtosis imaging probes cortical alterations and white matter pathology following cuprizone induced demyelination and spontaneous remyelination. *Neuroimage, 125*, 363-377. doi:https://doi.org/10.1016/j.neuroimage.2015.10.052

Hagiwara, A., Hori, M., Yokoyama, K., Nakazawa, M., Ueda, R., Horita, M., . . . Aoki, S. (2017). Analysis of White Matter Damage in Patients with Multiple Sclerosis via a Novel In Vivo MR Method for Measuring Myelin, Axons, and G-Ratio. *AJNR Am J Neuroradiol, 38*(10), 1934-1940. doi:10.3174/ajnr.A5312

Hagiwara, A., Kamagata, K., Shimoji, K., Yokoyama, K., Andica, C., Hori, M., . . . Aoki, S. (2019). White Matter Abnormalities in Multiple Sclerosis Evaluated by Quantitative Synthetic MRI, Diffusion Tensor Imaging, and Neurite Orientation Dispersion and Density Imaging. *AJNR Am J Neuroradiol, 40*(10), 1642-1648. doi:10.3174/ajnr.A6209

Huisman, T. A., Sorensen, A. G., Hergan, K., Gonzalez, R. G., & Schaefer, P. W. (2003). Diffusion-weighted imaging for the evaluation of diffuse axonal injury in closed head injury. *J Comput Assist Tomogr, 27*(1), 5-11. doi:10.1097/00004728-200301000-00002

Jelescu, I. O., Veraart, J., Adisetiyo, V., Milla, S. S., Novikov, D. S., & Fieremans, E. (2015). One diffusion acquisition and different white matter models: How does microstructure change in human early development based on WMTI and NODDI? *Neuroimage, 107*, 242-256. doi:https://doi.org/10.1016/j.neuroimage.2014.12.009

Jensen, J. H., Helpern, J. A., Ramani, A., Lu, H., & Kaczynski, K. (2005). Diffusional kurtosis imaging: The quantification of non-gaussian water diffusion by means of magnetic resonance imaging. *Magnetic Resonance in Medicine, 53*(6), 1432-1440. doi:https://doi.org/10.1002/mrm.20508

Lakhani, D. A., Schilling, K. G., Xu, J., & Bagnato, F. (2020). Advanced Multicompartment Diffusion MRI Models and Their Application in Multiple Sclerosis. *AJNR Am J Neuroradiol, 41*(5), 751-757. doi:10.3174/ajnr.A6484

Larsson, H. B., Thomsen, C., Frederiksen, J., Stubgaard, M., & Henriksen, O. (1992). In vivo magnetic resonance diffusion measurement in the brain of patients with multiple sclerosis. *Magn Reson Imaging, 10*(1), 7-12. doi:10.1016/0730-725x(92)90367-9

Li, H. Q., Yin, B., Quan, C., Geng, D. Y., Yu, H., Bao, Y. F., . . . Li, Y. X. (2018). Evaluation of patients with relapsing-remitting multiple sclerosis using tract-based spatial statistics analysis: diffusion kurtosis imaging. *BMC Neurology, 18*(1), 108. doi:10.1186/s12883-018-1108-2

McDonald, W. I., Compston, A., Edan, G., Goodkin, D., Hartung, H.-P., Lublin, F. D., . . . Wolinsky, J. S. (2001). Recommended diagnostic criteria for multiple sclerosis: Guidelines from the international panel on the diagnosis of multiple sclerosis. *Annals of Neurology, 50*(1), 121-127. doi:https://doi.org/10.1002/ana.1032

Mustafi, S. M., Harezlak, J., Kodiweera, C., Randolph, J. S., Ford, J. C., Wishart, H. A., & Wu, Y. C. (2019). Detecting white matter alterations in multiple sclerosis using advanced diffusion magnetic resonance imaging. *Neural Regen Res, 14*(1), 114-123. doi:10.4103/1673-5374.243716

Pagani, E., Bammer, R., Horsfield, M. A., Rovaris, M., Gass, A., Ciccarelli, O., & Filippi, M. (2007). Diffusion MR imaging in multiple sclerosis: technical aspects and challenges. *AJNR Am J Neuroradiol, 28*(3), 411-420.

Polman, C. H., Reingold, S. C., Banwell, B., Clanet, M., Cohen, J. A., Filippi, M., . . . Wolinsky, J. S. (2011).

Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol, 69*(2), 292-302. doi:10.1002/ana.22366

Polman, C. H., Reingold, S. C., Edan, G., Filippi, M., Hartung, H.-P., Kappos, L., . . . Wolinsky, J. S. (2005). Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Annals of Neurology, 58*(6), 840-846. doi:https://doi.org/10.1002/ana.20703

Qian, W., Chan, K. H., Hui, E. S., Lee, C. Y., Hu, Y., & Mak, H. K.-F. (2016). Application of diffusional kurtosis imaging to detect occult brain damage in multiple sclerosis and neuromyelitis optica. *NMR in Biomedicine, 29*(11), 1536-1545. doi:https://doi.org/10.1002/nbm.3607

Rosso, C., Remy, P., Creange, A., Brugieres, P., Cesaro, P., & Hosseini, H. (2006). Diffusion-weighted MR imaging characteristics of an acute strokelike form of multiple sclerosis. *AJNR Am J Neuroradiol, 27*(5), 1006-1008.

Rovira, À., Wattjes, M. P., Tintoré, M., Tur, C., Yousry, T. A., Sormani, M. P., . . . on behalf of the, M. s. g. (2015). MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis—clinical implementation in the diagnostic process. *Nature Reviews Neurology, 11*(8), 471-482. doi:10.1038/nrneurol.2015.106

Sacco, S., Caverzasi, E., Papinutto, N., Cordano, C., Bischof, A., Gundel, T., . . . Henry, R. G. (2020). Neurite Orientation Dispersion and Density Imaging for Assessing Acute Inflammation and Lesion Evolution in MS. *AJNR Am J Neuroradiol, 41*(12), 2219-2226. doi:10.3174/ajnr.A6862

Saeedi, J. A., AlYafeai, R. H., AlAbdulSalam, A. M., Al-Dihan, A. Y., AlDwaihi, A. A., Al Harbi, A. A., . . . Al Jumah, M. A. (2023). Saudi Consensus Recommendations on the Management of Multiple Sclerosis: Diagnosis and Radiology/Imaging. *Clinical and Translational Neuroscience, 7*(1), 5. Retrieved from https://www.mdpi.com/2514-183X/7/1/5

Schneider, T., Brownlee, W., Zhang, H., Ciccarelli, O., Miller, D. H., & Wheeler-Kingshott, C. G. (2017). Sensitivity of multi-shell NODDI to multiple sclerosis white matter changes: a pilot study. *Functional Neurology, 32*(2), 97-101. doi:10.11138/FNeur/2017.32.2.097

Simon, J. H., Li, D., Traboulsee, A., Coyle, P. K., Arnold, D. L., Barkhof, F., . . . Wolinsky, J. S. (2006). Standardized MR imaging protocol for multiple sclerosis: Consortium of MS Centers consensus guidelines. *AJNR Am J Neuroradiol, 27*(2), 455-461.

Spanò, B., Giulietti, G., Pisani, V., Morreale, M., Tuzzi, E., Nocentini, U., . . . Cercignani, M. (2018). Disruption of neurite morphology parallels MS progression. *Neurol Neuroimmunol Neuroinflamm, 5*(6), e502. doi:10.1212/nxi.0000000000000502

Stulík, J., Keřkovský, M., Kuhn, M., Svobodová, M., Benešová, Y., Bednařík, J., . . . Dostál, M. (2022). Evaluating Magnetic Resonance Diffusion Properties Together with Brain Volumetry May Predict Progression to Multiple Sclerosis. *Academic Radiology, 29*(10), 1493-1501. doi:https://doi.org/10.1016/j.acra.2021.12.015

Thompson, A. J., Banwell, B. L., Barkhof, F., Carroll, W. M., Coetzee, T., Comi, G., . . . Cohen, J. A. (2018). Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol, 17*(2), 162-173. doi:10.1016/s1474-4422(17)30470-2

Traboulsee, A., Simon, J. H., Stone, L., Fisher, E., Jones, D. E., Malhotra, A., . . . Li, D. (2016a). Revised Recommendations of the Consortium of MS Centers Task Force for a Standardized MRI Protocol and Clinical Guidelines for the Diagnosis and Follow-Up of Multiple Sclerosis. *AJNR Am J Neuroradiol, 37*(3), 394-401. doi:10.3174/ajnr.A4539

Traboulsee, A., Simon, J. H., Stone, L., Fisher, E., Jones, D. E., Malhotra, A., . . . Li, D. (2016b). Revised Recommendations of the Consortium of MS Centers Task Force for a Standardized MRI Protocol and Clinical Guidelines for the Diagnosis and Follow-Up of Multiple Sclerosis. *American Journal of Neuroradiology, 37*(3), 394. doi:10.3174/ajnr.A4539

Walton, C., King, R., Rechtman, L., Kaye, W., Leray, E., Marrie, R. A., . . . van Der Mei, I. (2020). Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS. *Multiple Sclerosis Journal, 26*(14), 1816-1821.

Wattjes, M. P., Ciccarelli, O., Reich, D. S., Banwell, B., de Stefano, N., Enzinger, C., . . . Rovira, À. (2021). 2021 MAGNIMS-CMSC-NAIMS consensus recommendations on the use of MRI in patients with multiple sclerosis. *Lancet Neurol, 20*(8), 653-670. doi:10.1016/s1474-4422(21)00095-8

Wattjes, M. P., Rovira, À., Miller, D., Yousry, T. A., Sormani, M. P., de Stefano, N., . . . on behalf of the, M. s. g. (2015). MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis—establishing disease prognosis and monitoring patients. *Nature Reviews Neurology, 11*(10), 597-606. doi:10.1038/nrneurol.2015.157

Wen, Q., Kelley, D. A. C., Banerjee, S., Lupo, J. M., Chang, S. M., Xu, D., . . . Nelson, S. J. (2015). Clinically feasible NODDI characterization of glioma using multiband EPI at 7 T. *NeuroImage: Clinical, 9*, 291-299. doi:https://doi.org/10.1016/j.nicl.2015.08.017

Wu, Y. C., Field, A. S., Duncan, I. D., Samsonov, A. A., Kondo, Y., Tudorascu, D., & Alexander, A. L. (2011). High b-value and diffusion tensor imaging in a canine model of dysmyelination and brain maturation. *Neuroimage, 58*(3), 829-837. doi:10.1016/j.neuroimage.2011.06.067