American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Mini Review



# Biomarkers of Neurodegenerative Disease using Diffusion Magnetic Resonance Imaging

**Yuya Saito***

*Department of Radiology, Juntendo University Graduate School of Medicine, Tokyo Japan*

***Corresponding author:** Yuya Saito, Department of Radiology, Juntendo University Graduate School of Medicine, Tokyo Japan

***To Cite This Article:*** *Yuya Saito. Biomarkers of Neurodegenerative Disease using Diffusion Magnetic Resonance Imaging. Am J Biomed Sci & Res. 2022 17(5) AJBSR.MS.ID.002392,* DOI: 10.34297/AJBSR.2022.17.002392

**Received:** December 05, 2022; **Published:** December 21, 2022

## Abstract

With the significant global growth in the number of aging societies, neurological illnesses have become more prevalent. Urgently required are biomarkers that may be utilized to identify pathological alterations prior to the onset of severe neuronal loss and hence permit early intervention with disease-modifying treatment approaches. Diffusion magnetic resonance imaging (MRI) is a promising technique that can be used to infer microstructural characteristics of the brain, including microstructural integrity and complexity, as well as axonal density, order, and myelination, by utilizing water molecules that are diffused within the tissue, with displacement at the micron scale. For assessing the pathophysiology of neurodegenerative disorders, diffusion tensor imaging is the most used diffusion MRI method. New methods, such as neurite orientation dispersion and density imaging, diffusion kurtosis imaging, and free-water imaging, have been developed to circumvent the limitations of diffusion tensor imaging. This article presents an overview of these technologies and their potential as biomarkers for the early diagnosis and development of significant neurodegenerative illnesses.

**Keywords:** Biomarker, Diffusion Kurtosis Imaging, Diffusion Tensor Imaging, Free-water Imaging, Neurite Orientation Dispersion and Density Imaging, Alzheimer's Disease, Parkinson's Disease

## Introduction

The frequency of neurodegenerative illnesses is rising in tandem with the fast aging of the world's civilizations. Alzheimer's disease (AlzD) and Parkinson's disease (PD), two of the most prevalent neurodegenerative illnesses, are estimated to affect 35 million [1] and 6 million [2] persons worldwide, respectively. Importantly, it is anticipated that the prevalence rates of neurodegenerative disorders would climb even more quickly as the world population ages, given that aging is a key risk factor for these illnesses, signifying a rising public health concern. Neurodegenerative disorders presently have no curative treatments; consequently, the discovery of disease-modifying medications that may halt the progression of underlying pathological alterations is eagerly awaited. Urgently required are biomarkers that may be utilized to identify pathological alterations prior to the onset of severe neuronal loss and therefore permit early intervention with disease-modifying treatment methods. Among the several possible biomarkers that have been suggested, magnetic resonance imaging (MRI) is an outstanding candidate biomarker, since it provides a potent method for noninvasive *in vivo* brain examination. Specifically, diffusion MRI is promising because it can infer microstructural characteristics of the brain, such as microstructural integrity and complexity, as well as axonal density, order, and myelination, by utilizing water molecules that diffuse within the tissue with micron-scale displacement [3]. Neurite orientation dispersion and density imaging (NODDI), diffusion kurtosis imaging (DKI), and free-water imaging (FWI) have been developed as alternatives to DTI. Diffusion tensor imaging (DTI) is the most commonly used diffusion MRI technique to assess pathophysiology in neurodegenerative diseases (see Table 1 for summary). This article presents an overview of these technologies and their potential as biomarkers for early neurodegenerative disease diagnosis and progression prevention.

## Diffusion MRI Techniques

### DTI

The biologically structured structure of the brain, including axons, myelin, cerebrospinal fluid (CSF), and neuronal soma and dendrites, influences water diffusion in the brain. Isotropic diffusion, in which water diffuses equally in all directions (e.g., in cerebrospinal fluid (CSF) and gray matter (GM)), may be distinguished from anisotropic diffusion, in which water diffusion is unidirectional (e.g., in white matter (WM)). The uses and efficacy of DTI in brain illnesses have been discussed earlier [3,4]. DTI characterizes brain structures on the basis of water diffusion using four metrics: fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) [5].

DTI is applied extensively in neurodegenerative illnesses such as Alzheimer's disease [6-8], Parkinson's disease [9-12], multiple sclerosis [13-15], stroke, and traumatic brain injury [16-18]. However, a number of deficiencies restrict its clinical applicability. First, DTI can not account for the non-Gaussian diffusion characteristics of water molecules in some biological tissue components, such as the cell membrane and myelin sheath, which results in biological limitations [19,20]. Therefore, DTI is incapable of detecting microstructural changes in GM, which is mostly constituted of neuronal cell bodies and displays greater isotropic water transport [19,20]. Second, DTI assumes that each voxel contains a single tissue compartment, which creates a partial volume effect due to the presence of extracellular free water, such as CSF [5] and significantly affects the accuracy of DTI measurements at the GM/WM boundary [21,22] and that of the GM voxels contaminated by CSF [23,24]. Third, DTI parameters lack disease-specific and pathological information [3]. For instance, it is unclear whether a drop in FA means a reduction in axon density or axon-bundle cross-section, and the interpretation of DTI parameters [25-28] is contentious. In conclusion, the DTI model oversimplifies the brain's anatomy. Despite the fact that WM voxels include crossing fibers and account for up to 90% of all adult brain voxels [29,30], DTI reflects only a single major direction; thus, FA diminishes in such voxels even in normal brain tissue [31].

### DKI

A mathematical extension of DTI, DKI was suggested. Kurtosis is dimensionless [19,20] and assesses the degree of non-Gaussian distribution in water diffusion inside a voxel. Consequently, DKI identifies the limitation of water transport caused by the intricacy of brain tissue components such as the cell membrane and myelin sheath [32]. The greater the diffusion kurtosis, the greater the deviation of water molecule diffusion from the Gaussian distribution, indicating a more constrained diffusion environment. In contrast, a lower diffusion kurtosis indicates less limited diffusion, such as in neuronal degeneration [33].

DKI needs at least three b-values and 15 diffusion gradient directions for a more complicated model [34]. DTI requires at least two b-values and six diffusion gradient directions. DKI measures the condition of brain tissue via the use of three kurtosis metrics: mean kurtosis (MK), axial kurtosis (AK), and radial kurtosis (RK) (RK). DKI has been used to assess neurodegeneration in WM with complex architectures, including voxels with crossing fibers [12,35-37]. Moreover, DKI parameters reflect the restriction of water diffusion in anisotropic as well as isotropic environments, in contrast to DTI parameters, which assume non-restriction of water diffusion; thus, the utility of DKI has also been demonstrated for the evaluation of microstructural changes in GM, which is primarily composed of neuronal cell bodies and exhibits isotropic water diffusion [20,28,38,39].

Despite its advantage over DTI for the assessment of diseased brain alterations, DKI has numerous drawbacks. First, the acquisition time of DKI (about 10 minutes) is greater than that of DTI (roughly 5 minutes) [19,40], which reduces its clinical value since the more sophisticated DKI model needs more parameters than DTI. Because neither model involves biophysical assumptions [19,20], neither DKI nor DTI can explain disease-specific and pathological alterations such as the density, dispersion, and cross-section of axons or dendrites in neurons.

### FWI

As explained in Section 2.1, DTI can reliably estimate tissue-specific indices only in voxels containing a single kind of brain tissue, but cannot quantify tissue-specific indices in voxels polluted by extracellular free water, such as CSF [5,21-24]. FWI was first suggested for the distinct interpretation of microstructures inside brain tissue and extracellular fluid within the same voxel [41]. FWI is a two-compartment (or bi-tensor) model consisting of anisotropic brain tissue and isotropic free water. After eliminating extracellular free water contamination, FWI calculates the free water volume fraction (FW) map with the free water compartment and the traditional DTI map with the tissue compartment [41]. Thus, FWI may increase the accuracy of single-tensor DTI indices and analyzes particularly the microstructures of brain tissue after the removal of free water. Moreover, the free-water map is regarded as a potential biomarker for discriminating between neuronal degeneration and the increase of free water in the extracellular space, which is linked to neuronal disorders such as neuroinflammation [41-43]. FWI can quantitatively measure the degree of edema and atrophy, as well as neuroinflammation, and hence may contribute to a better understanding of the pathophysiology underlying neurodegenerative illnesses such as Parkinson's disease [42], schizophrenia [44,45], and depression [46].

FWI may be estimated from clinically common single-shell diffusion data using the same method as DTI [41], and its accuracy is equivalent to that obtained from multi-shell diffusion data [47]. Nonetheless, the estimate of FWI is highly dependent on the regularization restrictions of spatial smoothing, which may result in decreased sensitivity for modest diseases [41,47]. Other approaches that do not need spatial regularization may be able to reconstruct more accurate FWI indices [47,48] when multishell diffusion acquisition is employed to estimate FWI.

### NODDI

NODDI was designed to provide a more precise description of brain tissue microstructures than signal representations like DTI and DKI. NODDI simulates three compartments of brain tissue. The intracellular compartment corresponds to the space bordered by the neurite membrane, the extracellular compartment to the space surrounding by neurites, and the isotropic water pool to the space filled by CSF [49]. Before NODDI, other methods that assume numerous compartments, such as the composite hindered and limited water diffusion (CHARMED) model [50,51], were created. NODDI's innovation, however, is in its capacity to reveal the properties of angular variances of neurites inside each voxel. NODDI not only quantifies the isotropic volume fraction (ISOVF, volume fraction of extracellular isotropic free water), but also the orientation dispersion index (ODI, index of intracellular neurite dispersion) and the intracellular volume fraction (ICVF, neurite density) [49,52]. After the elimination of extracellular free water from the voxel, ICVF and ODI may thereby characterize the biological microstructures of axons and dendrites. In addition, an increased ISOVF in WM may potentially account for neurodegeneration accompanied by an increase in extracellular isotropic fluid, such as in neuroinflammation [49].

Consequently, NODDI may be utilized to represent microstructures more precisely than signal representation approaches [49,53,54], notwithstanding NODDI's limitations. First, whereas ODI is very accurate at predicting single-shell diffusion data, ICVF and ISOVF need multi-shell diffusion data with a minimum of two shells [49,55], comparable to DKI. Therefore, a lengthy acquisition period is required for estimating neurite density and extracellular fluid. Second, while the anisotropic orientation dispersion of neurites induced by bending and fanning fibers is seen across the whole brain [56], NODDI cannot assess the complicated anisotropic neurite dispersion since it models only the isotropic neurite dispersion.

## Conclusion and Future Directions

Neurodegenerative illnesses have been elucidated by the use of advanced diffusion MRI methods, such as FWI, DKI, and NODDI, which give novel information on brain microstructures. Due to the absence of clinical proof of their efficacy, these sophisticated approaches have not yet been used in clinical settings, such as the regular use of DWI to evaluate myocardial infarction. In addition, unlike the measurement of hippocampal volume, a biomarker for Alzheimer's disease that is used to reduce the sample size and cost of clinical trials for the detection of neurodegenerative changes [57], the evidence regarding the utility of advanced diffusion MRI-based biomarkers in neurodegenerative diseases is insufficient. Clinical trials are impeded by the high costs involved with conducting them. Consequently, the cost-effectiveness of newer diffusion MRI methods hinders the gathering of clinical data.

To accomplish the practical use of sophisticated diffusion MRI methods for the diagnosis of neurodegenerative disorders, many obstacles must be overcome. First, the link between pathological alterations in neurodegenerative illnesses and improved diffusion MRI measures is yet unknown. DKI, FWI, and NODDI only model and forecast brain microstructures via diffusion MRI, and it is uncertain to what degree these models can reflect and explain particular neurodegenerative illnesses. In order to understand the association between pathological results and the advanced diffusion MRI metrics of FWI, DKI, and NODDI, more investigations on neurodegenerative disorders in postmortem human tissues or animal models are required. Second, the repeatability and dependability of the findings of research using sophisticated diffusion MRI methods are extremely poor due to the small sample sizes and thus low statistical power. Therefore, it is necessary to show the efficacy of FWI, DKI, and NODDI as biomarkers for neurodegenerative illnesses based on robust evidence from multi-site studies with greater sample numbers to increase their statistical power. Although a number of large-scale multi-site investigations are now ongoing, MRI scanners and acquisition settings are very variable and site-dependent [58]. These variations across research locations may reduce the repeatability and reliability of sophisticated MRI diffusion investigations. Andica *et al*. [59] assessed the scan-rescan and inter-vendor repeatability of DTI and NODDI using two 3-T MRI scanners from two manufacturers. The scan-rescan coefficient of variation of NODDI measurements with both scanners was close to that of DTI metrics (0.2% to 3.8%). However, the inter-vendor CoV for NODDI measurements was greater than the scan-rescan CoV (2.3-14%). In addition, the inter-sequence variability of DTI measurements for three distinct sequences revealed that the CoVs for FA and MD were 5.45-7.34% and 1.72-5.55%, respectively [60]. In addition, Kamagata *et al*. [61] assessed the inter-site reproducibility of DTI measurements using identical 3-T MRI scanners and acquisition conditions at two distinct locations. According to the authors, the CoV of DTI varied from 0.6% to 5.6%. Consequently, changes in diffusion MRI metrics induced by site differences, such as MRI scanners and acquisition settings, may impair their statistical power, resulting

in poor repeatability and reliability in multi-site studies using sophisticated diffusion MRI methods [58]. Specifically, changes in diffusion MRI metrics in neurocognitive and psychiatric disorders are subtle (approximately 5-6%) compared to healthy controls and on the same order as that of site difference; thus, it is challenging for a multi-site study to detect pathological changes in patients with neurocognitive and psychiatric disorders [62-64]. Therefore, it is vital to decrease inter-site variability in diffusion MRI metrics by harmonizing multi-site diffusion MRI data and standardizing MRI procedures, including MRI scanners and acquisition settings. Several harmonization strategies for diffusion MRI, such as the combined association test ComBat [65], linear regression based on rotation-invariant spherical harmonics [66], and the deep learning approach [67], have been suggested to decrease the variance across MRI scanners and protocols. ComBat utilizes the regression of variables for the data harmonization of diffusion MRI measurements using an empirical Bayesian inference. The linear rotation invariant spherical harmonics are used for diffusion MRI signal harmonization and mapping of diffusion MRI data from a target location to a reference site. The deep learning harmonization technique optimizes neural network parameters using diffusion MRI signals received from target and reference locations during the learning phase, and then uses the trained neural network to harmonize diffusion MRI data. These harmonization strategies not only eliminate undesirable fluctuations in DTI measures caused by site differences, but they also retain biological diversity caused by age and gender.

Another issue is the unknown link between neurodegenerative disease-induced pathological alterations and advanced diffusion MRI measurements. DKI, FWI, and NODDI can only model and forecast brain microstructures using diffusion MRI, and it is uncertain to what degree these models represent and explain particular neurodegenerative illnesses. In order to understand the association between pathological results and the advanced diffusion MRI metrics of DKI, FWI, and NODDI, more research of neurodegenerative illnesses in postmortem human tissues or animal models are necessary. Resolving these constraints should result in the practical use of enhanced diffusion MRI methods as diagnostic biomarkers for neurodegenerative disorders.

Recently, frameworks that integrate diffusion tensor MRI and relaxometry have been developed to increase their specificity for quantifying myelin and axonal characteristics regardless of the complexity of fiber organization inside the voxel, even in the presence of crossing fibers [68,69]. In addition, accumulating evidence implicates excessive iron accumulation in the pathogenesis of neurodegenerative disorders [70]. Quantitative susceptibility mapping is a potential imaging tool for the complete study of iron distribution in the brain. By assessing various biological tissue qualities, the use of the diffusion tensor-relaxometry framework or the combination of modern diffusion MRI methods and quantitative susceptibility mapping may offer a more complete picture of neurodegenerative disorders.

## References


1. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, *et al* (2013) The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement 9(1): 63-75.

2. Dorsey ER, Elbaz A, Nichols E, Abbasi N, Abd Allah F, *et al* (2018) Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol Elsevier 17(11): 939-953.

3. Assaf Y, Pasternak O (2008) Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review J Mol Neurosci Springer 34: 51-61.

4. Mori S, Zhang J (2006) Principles of diffusion tensor imaging and its applications to basic neuroscience research Neuron 51(5): 527-539.

5. Alexander AL, Lee JE, Lazar M, Field AS (2007) Diffusion tensor imaging of the brain. Neurotherapeutics 4(3): 316-329.

6. Clerx L, Visser PJ, Verhey F, Aalten P (2012) New MRI markers for Alzheimer's disease: a meta-analysis of diffusion tensor imaging and a comparison with medial temporal lobe measurements J Alzheimers Dis 29(2): 405-429.

7. Sexton CE, Kalu UG, Filippini N, Mackay CE, Ebmeier KP (2011) A meta-analysis of diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease. Neurobiol Aging 32(12): 2322. e5-18.

8. Teipel SJ, Wegrzyn M, Meindl T, Frisoni G, Bokde ALW *et al* (2012) Anatomical MRI and DTI in the diagnosis of Alzheimer's disease: a European multicenter study. J Alzheimers Dis 31 Suppl 3: S33-47.

9. Atkinson Clement C, Pinto S, Eusebio A, Coulon O (2017) Diffusion tensor imaging in Parkinson's disease: Review and meta-analysis. Neuroimage Clin 16: 98-110.

10. Cochrane CJ, Ebmeier KP (2013) Diffusion tensor imaging in parkinsonian syndromes: a systematic review and meta-analysis. Neurology 80(9): 857-864.

11. Guimarães RP, Campos BM, De Rezende TJ, Piovesana L, Azevedo PC, *et al* (2018) Is Diffusion Tensor Imaging a Good Biomarker for Early Parkinson's Disease? Front Neurol 9:626.

12. Kamagata K, Tomiyama H, Hatano T, Motoi Y, Abe O, *et al* (2014) A preliminary diffusional kurtosis imaging study of Parkinson disease: comparison with conventional diffusion tensor imaging. Neuroradiology 56(3): 251-258.

13. Hagiwara A, Kamagata K, Shimoji K, Yokoyama K, Andica C, *et al* (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.

14. Rovaris M, Agosta F, Pagani E, Filippi M (2009) Diffusion tensor MR imaging. Neuroimaging Clin N Am 19: 37-43.

15. Rovaris M, Filippi M (2007) Diffusion tensor MRI in multiple sclerosis. J Neuroimaging 17 Suppl 1: 27S - 30S.

16. Dodd AB, Epstein K, Ling JM, Mayer AR (2014) Diffusion tensor imaging findings in semi-acute mild traumatic brain injury. J Neurotrauma 31(14): 1235-1248.

17. Lo C, Shifteh K, Gold T, Bello JA, Lipton ML (2009) Diffusion tensor imaging abnormalities in patients with mild traumatic brain injury and neurocognitive impairment. J Comput Assist Tomogr 33(2): 293-297.

18. Niogi SN, Mukherjee P (2010) Diffusion tensor imaging of mild traumatic brain injury. J Head Trauma Rehabil. Journals lww com 25(4):241-255.

19. Jensen JH, Helpern JA (2010) MRI quantification of non-Gaussian water diffusion by kurtosis analysis. NMR Biomed 23(7): 698-710.

20. Jensen JH, Helpern JA, Ramani A, Lu H, Kaczynski K (2005) Diffusional kurtosis imaging: the quantification of non-gaussian water diffusion by means of magnetic resonance imaging. Magn Reson Med 53(6): 1432-1440.

21. Shimony JS, McKinstry RC, Akbudak E, Aronovitz JA, Snyder AZ, *et al* (1999) Quantitative diffusion-tensor anisotropy brain MR imaging: normative human data and anatomic analysis. Radiology 212(3): 770-784.

22. Zacharopoulos NG, Narayana PA (1998) Selective measurement of white matter and gray matter diffusion trace values in normal human brain. Med Phys 25(11): 2237-2241.

23. Falconer JC, Narayana PA (1997) Cerebrospinal fluid-suppressed high-resolution diffusion imaging of human brain. Magn Reson Med Wiley 37(1): 119-123.

24. Hirsch JG, Bock M, Essig M, Schad LR (1999) Comparison of diffusion anisotropy measurements in combination with the flair-technique. Magn Reson Imaging 17(5): 705-716.

25. Beaulieu C (2002) The basis of anisotropic water diffusion in the nervous system - a technical review. NMR Biomed Wiley 15(7-8): 435-455.

26. Chung AW, Seunarine KK, Clark CA (2016) NODDI reproducibility and variability with magnetic field strength: A comparison between 1.5 T and 3 T. Hum Brain Mapp 37(12): 4550-4565.

27. Wheeler Kingshott CAM, Cercignani M (2009) About "axial" and "radial" diffusivities. Magn Reson Med Wiley 61(5): 1255-1260.

28. Kamagata K, Zalesky A, Hatano T, Ueda R, Di Biase MA, (2017) Gray Matter Abnormalities in Idiopathic Parkinson's Disease: Evaluation by Diffusional Kurtosis Imaging and Neurite Orientation Dispersion and Density Imaging. Hum Brain Mapp 38(7): 3704-3722.

29. Behrens TEJ, Berg HJ, Jbabdi S, Rushworth MFS, Woolrich MW (2007) Probabilistic diffusion tractography with multiple fibre orientations: What can we gain? Neuroimage. 34(1):144-155.

30. Jeurissen B, Leemans A, Tournier JD, Jones DK, Sijbers J (2013) Investigating the prevalence of complex fiber configurations in white matter tissue with diffusion magnetic resonance imaging. Hum Brain Mapp 34(11): 2747-2766.

31. Tournier JD, Mori S, Leemans A (2011) Diffusion tensor imaging and beyond. Magn Reson Med 65(6): 1532-1556.

32. Steven AJ, Zhuo J, Melhem ER (2014) Diffusion kurtosis imaging: an emerging technique for evaluating the microstructural environment of the brain. AJR Am J Roentgenol 202(1): W26-W33.

33. Arab A, Wojna Pelczar A, Khairnar A, Szabó N, Ruda Kucerova J (2018) Principles of diffusion kurtosis imaging and its role in early diagnosis of neurodegenerative disorders. Brain Res Bull 139: 91-98.

34. Jelescu IO, Budde MD (2017) Design and validation of diffusion MRI models of white matter. Front Phys [Internet] 28.

35. Hattori A, Kamagata K, Kirino E, Andica C, Tanaka S, *et al* (2019) White matter alterations in adult with autism spectrum disorder evaluated using diffusion kurtosis imaging. Neuroradiology 61(12): 1343-1353.

36. Kamagata K, Motoi Y, Tomiyama H, Abe O, Ito K, *et al* (2013) Relationship between cognitive impairment and white-matter alteration in Parkinson's disease with dementia: tract-based spatial statistics and tract-specific analysis. Eur Radiol 23(7): 1946-1955.

37. Kamiya K, Kamagata K, Ogaki K, Hatano T, Ogawa T, Takeshige Amano H (2020) Brain White-Matter Degeneration Due to Aging and Parkinson Disease as Revealed by Double Diffusion Encoding. Front Neurosci 14: 584510.

38. Andica C, Kamagata K, Hatano T, Saito Y, Ogaki K, *et al* (2020) MR Biomarkers of Degenerative Brain Disorders Derived From Diffusion Imaging. J Magn Reson Imaging 52(6): 1620-1636.

39. Lu H, Jensen JH, Ramani A, Helpern JA (2006) Three-dimensional characterization of non-gaussian water diffusion in humans using diffusion kurtosis imaging. NMR Biomed Wiley 19(2): 236-247.

40. Szczepankiewicz F, Lätt J, Wirestam R, Leemans A, Sundgren P, *et al* (2013) Variability in diffusion kurtosis imaging: impact on study design, statistical power and interpretation. Neuroimage 76: 145-154.

41. Pasternak O, Sochen N, Gur Y, Intrator N, Assaf Y (2009) Free water elimination and mapping from diffusion MRI. Magn Reson Med 62(3): 717-730.

42. Andica C, Kamagata K, Hatano T, Saito A, Uchida W, *et al* (2019) Free-Water Imaging in White and Gray Matter in Parkinson's Disease. Cells 8(8): 839.

43. Oestreich LKL, Lyall AE, Pasternak O, Kikinis Z, Newell DT, *et al* (2017) Characterizing white matter changes in chronic schizophrenia: A free-water imaging multi-site study. Schizophr Res 189:153-161.

44. Lyall AE, Pasternak O, Robinson DG, Newell D, Trampush JW *et al* (2018) Greater extracellular free-water in first-episode psychosis predicts better neurocognitive functioning. Mol Psychiatry 23(3): 701-707.

45. Pasternak O, Westin CF, Bouix S, Seidman LJ, Goldstein JM, *et al* (2012) Excessive extracellular volume reveals a neurodegenerative pattern in schizophrenia onset. J Neurosci 32(48): 17365-17372.

46. Bergamino M, Pasternak O, Farmer M, Shenton ME, Hamilton JP (2016) Applying a free-water correction to diffusion imaging data uncovers stress-related neural pathology in depression. Neuroimage Clin 10: 336-342.

47. Pasternak O, Shenton ME, Westin CF (2012) Estimation of extracellular volume from regularized multi-shell diffusion MRI. Med Image Comput Comput Assist Interv 15(2): 305-312.

48. Hoy AR, Koay CG, Kecskemeti SR, Alexander AL (2014) Optimization of a free water elimination two-compartment model for diffusion tensor imaging. Neuroimage 103:323-333.

49. Zhang H, Schneider T, Wheeler Kingshott CA, Alexander DC (2012) NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain. Neuroimage 61(4): 1000-1016.

50. Assaf Y, Basser PJ (2005) Composite hindered and restricted model of diffusion (CHARMED) MR imaging of the human brain. Neuroimage 27(1): 48-58.

51. Assaf Y, Freidlin RZ, Rohde GK, Basser PJ (2004) New modeling and experimental framework to characterize hindered and restricted water diffusion in brain white matter [Internet]. Magnetic Resonance in Medicine 52(5): 965-978.

52. Zhang H, Hubbard PL, Parker GJM, Alexander DC (2011) Axon diameter mapping in the presence of orientation dispersion with diffusion MRI. Neuroimage 56(3):1301-1315.

53. Grussu F, Schneider T, Tur C, Yates RL, Tachrount M, *et al* (2017) Neurite dispersion: a new marker of multiple sclerosis spinal cord pathology? Ann Clin Transl Neurol 4(9): 663-679.

54. Schilling KG, Janve V, Gao Y, Stepniewska I, Landman BA, (2018) Histological validation of diffusion MRI fiber orientation distributions and dispersion. Neuroimage 165:200-221.

55. Parvathaneni P, Nath V, Blaber JA, Schilling KG, Hainline AE, *et al* (2018) Empirical reproducibility, sensitivity, and optimization of acquisition protocol, for Neurite Orientation Dispersion and Density Imaging using AMICO. Magn Reson Imaging 50: 96-109.

56. Tariq M, Schneider T, Alexander DC, Gandini Wheeler-Kingshott CA, Zhang H (2016) Bingham-NODDI: Mapping anisotropic orientation dispersion of neurites using diffusion MRI. Neuroimage 133: 207-223.

57. Yu P, Sun J, Wolz R, Stephenson D, Brewer J, *et al* (2014) Operationalizing hippocampal volume as an enrichment biomarker for amnestic mild cognitive impairment trials: effect of algorithm, test-retest variability, and cut point on trial cost, duration, and sample size. Neurobiol Aging 35(4): 808-818.

58. Zhu T, Hu R, Qiu X, Taylor M, Tso Y, *et al* (2011) Quantification of accuracy and precision of multi-center DTI measurements: a diffusion phantom and human brain study. Neuroimage 56(3): 1398-1411.

59. Andica C, Kamagata K, Hayashi T, Hagiwara A, Uchida W, *et al* (2020) Scan-rescan and inter-vendor reproducibility of neurite orientation dispersion and density imaging metrics. Neuroradiology 62(4): 483-494.

60. Cercignani M, Bammer R, Sormani MP, Fazekas F, Filippi M (2003) Inter-sequence and inter-imaging unit variability of diffusion tensor MR imaging histogram-derived metrics of the brain in healthy volunteers. AJNR Am J Neuroradiol 24(4): 638-643.

61. Kamagata K, Shimoji K, Hori M, Nishikori A, Tsuruta K, *et al* (2015) Intersite Reliability of Diffusion Tensor Imaging on Two 3T Scanners. Magn Reson Med Sci jstage jst go jp 14(3): 227-233.

62. Mahoney CJ, Simpson IJA, Nicholas JM, Fletcher PD, Downey LE, *et al* (2015) Longitudinal diffusion tensor imaging in frontotemporal dementia. Ann Neurol. Wiley Online Library 77(1) : 33-46.

63. Tu MC, Lo CP, Huang CF, Hsu YH, Huang WH, *et al* (2017) Effectiveness of diffusion tensor imaging in differentiating early-stage subcortical ischemic vascular disease, Alzheimer's disease and normal ageing. PLoS One journals plos org 12(4): e0175143.

64. Voineskos AN, Lobaugh NJ, Bouix S, Rajji TK, Miranda D, *et al* (2010) Diffusion tensor tractography findings in schizophrenia across the adult lifespan. Brain academic oup com 133(5): 1494-1504.

65. Fortin JP, Parker D, Tunç B, Watanabe T, Elliott MA, *et al* (2017) Harmonization of multi-site diffusion tensor imaging data. Neuroimage. Elsevier 161: 149-170.

66. Cetin Karayumak S, Bouix S, Ning L, James A, Crow T, *et al* (2019) Retrospective harmonization of multi-site diffusion MRI data acquired with different acquisition parameters. Neuroimage Elsevier 184: 180-200.

67. Tax CM, Grussu F, Kaden E, Ning L, Rudrapatna U, *et al* (2019) Cross-scanner and cross-protocol diffusion MRI data harmonisation: A benchmark database and evaluation of algorithms. Neuroimage Elsevier 195(15): 285-299.

68. De Santis S, Barazany D, Jones DK, Assaf Y (2016) Resolving relaxometry and diffusion properties within the same voxel in the presence of crossing fibres by combining inversion recovery and diffusion-weighted acquisitions. Magn Reson Med 75(1): 372- 380.

69. Reymbaut A, Critchley J, Durighel G, Sprenger T, Sughrue M, *et al* (2021) Toward nonparametric diffusion- T1 characterization of crossing fibers in the human brain. Magn Reson Med 85(5): 2815-2827.

70. Ravanfar P, Loi SM, Syeda WT, Van Rheenen TE, Bush AI, *et al* (2021) Systematic Review: Quantitative Susceptibility Mapping (QSM) of Brain Iron Profile in Neurodegenerative Diseases. Front Neurosci 15: 618435.