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Review of Diffusion MRI Studies in Chronic White Matter Diseases

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Abstract

Diffusion MRI studies characterizing the changes in white matter (WM) due to vascular cognitive impairment, which includes all forms of small vessel disease are reviewed. We reviewed the usefulness of diffusion methods in discriminating the affected WM regions and its relation to cognitive impairment. These studies were categorized based on the diffusion MRI techniques used. The most common method was the diffusion tensor imaging, whereas other methods included diffusion weighted imaging, diffusion kurtosis imaging, intravoxel incoherent motion, and studies based on diffusion tractography. The diffusion measures showed correlation with cognitive scores and disease progression, with mean diffusivity being the most robust parameter. Future studies should focus on incorporating multi-compartment and higher order diffusion models, which can handle the presence of multiple and crossing fibers inside a voxel.

Keywords

White Matter diseases; Vascular cognitive imapairment and dementia; Cerebral small vessel diseases; Diffusion MRI

1. Introduction

In the late 1800s, Otto Binswanger was the first to describe pathological changes in the white matter (WM) in patients with dementia [1]. This contrasted with the neuronal damage in the cortex described around the same time by Alois Alzheimer. Interest in the WM pathology waned with few reports published on Binswanger's disease until the invention of modern neuroimaging methods. This contrasted to a growing interest in Alzheimer's disease (AD), which was observed pathologically in patients with dementia. With the invention of tomographic methods that were first applied to x-rays in computed tomography (CT) and shortly afterwards to magnetic resonance imaging (MRI), visualization of WM became

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routine in neurological diagnosis, and Binswanger's disease was more frequently diagnosed [2, 3], resulting in an "epidemic" of the disease by 1981, according to the medical journal the Lancet.[4]. Pathological changes in the subcortical regions of the brain were now recognized as a major contributor to dementia, resulting in a dramatic rise in interest vascular cognitive impairment and dementia [5]. As a result of the revival of interest in the WM, one hundred years after its original description, our understanding of the optimal ways to image the WM and the underlying pathophysiology of chronic vascular disease has greatly expanded, culminating in the development of diffusion-based methods to determine the integrity of the WM. The ability to determine the pathological state of the WM during life has led to dramatic advances in our understanding of the role of the WM in dementia [6]. Advances in imaging methods related to diffusion have grown so rapidly that they had out distanced the clinical conditions. This review will focus on MRI methods to assess changes in WM that through imaging reveal aspects of the underlying pathobiology.

Diffusion imaging is able to more accurately define the condition of the WM fiber tracts than conventional Fluid Attenuated Inversion Recovery (FLAIR) sequences used in routine clinical studies. Elderly individuals have a high incidence of WM hyperintensities (WMHs) on MRI [7]. While WMHs tend to correlate with cognitive decline, a significant number of healthy elderly have WMHs that increase in size with age [8]. Separating the pathological WM changes from those in normal individuals can be difficult with FLAIR MRI. This is the challenge faced by diffusion MRI, which more clearly delineates the pathological changes in WM. The problem is that there are many diffusion methods and the optimal ones are still being uncovered. Because the field is in flux, this review will describe a number of studies without attempting to choose the optimal method. In the past several years, a number of novel methods diffusion imaging have been tested and are now ready to enter use in clinical studies. This review will contrast and compare various diffusion MRI methods related to chronic WM diseases.

1.1. Diagnosis of patients with chronic WM disease

In the last ten years the MRI methods used to study cerebral small vessel disease (SVD) have been reviewed by multiple groups [9–16]. The MRI biomarkers used to study SVD are similar to those used for studying other neurodegenerative diseases, such as AD. The two diseases SVD and AD can coexist with aging to cause mixed dementia (MX). The terminology used in classifying different forms of dementia and the terminology of the MRI methods across different studies has been previously reviewed to encourage more standard data reporting [16]. In this review, while reporting on different studies, we retain the terminology used by the respective authors. Multiple infarcts (MI) are patients with large cerebrovascular infarcts either due to large vessel thrombosis or embolus. Since these patients often have atherosclerosis of the carotid arteries or atrial fibrillation, they have strokes at random intervals, making it difficult to determine the natural history. There are a smaller number of patients with MI. We have excluded the studies related to this group from the review unless they are a part of a SVD study.

There is a spectrum of diseases that result in changes in the WM, creating a challenge to the clinician to identify those patients with axonal injury that are at risk of progression. At one

end of the spectrum are WM changes of aging without pathological changes in the WM often associated with long-standing hypertension. When the WMHs on FLAIR are extensive without a clear underlying pathological process, the term leukoaraiosis (LA) can be used [17]. Pathological injury with loss of myelin can be detected by MRI with proton magnetic resonance spectroscopy (^{1}H-MRS) with low levels of N-ascetylaspartate (NAA) in regions with damaged axons. Low values for NAA can be used as a surrogate marker for WM injury [18]. Diffusion provides another measure of WM injury as shown by elevated mean diffusivity (MD) and reduced fractional anisotropy (FA). Subcortical ischemic vascular disease (SIVD) is used to describe large WM lesions secondary to SVD, which can be identified by either reduced NAA or elevated MD. Finally, there are patients with WMHs that have both AD probably secondary to neuronal loss and vascular disease similar to SIVD, which are called MX. Both AD and MX patients have reduced amyloid-$\beta_{1–42}$ / amyloid- $\beta_{1–40}$ ratio and elevated phospho-tau$_{181}$ in the CSF, and have deficits in memory function. Those with pure AD lack WMHs and have no neurological findings.

Patients with the diagnosis of SIVD generally have vascular risk factors with SVD secondary to hypertension, diabetes, hyperlipidemia, and sleep apnea. They often have asymmetric hyperreflexia and impaired balance with a tendency to fall. There may be lacunar strokes in the WM, and progression tends to be slow with gradual enlargement of the WM lesions. Cerebrospinal fluid (CSF) shows an increase in albumin index (ratio of albumin in CSF to that in blood), and amyloid-$\beta_{1–42}$ and phosphoTau in the CSF are normal. MX is a term used to describe patients that have evidence of AD as shown in reduced amyloid-$\beta_{1–42}$/amyloid-$\beta_{1–40}$ ratio in the CSF along with elevated phospho-tau$_{181}$. In addition, they have abnormal diffusion in the WM, indicating that that they have both AD and SIVD. Clinically, they have reduced memory function similar to AD and increased albumin ratio similar to SIVD. LA patients have large WMHs on FLAIR. However, diffusion is generally normal. The neuropsychological findings show normal function or mild cognitive impairment. This is an unstable group and can progress over time to either SIVD or MX.

2. MRI methods in VCI

Several MRI biomarkers have been used to study WM disease. They range from biomarkers implemented on standard clinical scanners which can be used across multiple sites and advanced methods requiring special techniques. Clinically applicable MRI biomarkers include small subcortical infarctions, lacunes of presumed vascular origins, WMHs of presumed vascular origin, perivascular spaces, cerebral microbleeds, and brain atrophy [15, 16]. The more advanced MRI biomarkers include blood-brain barrier permeability, magnetic resonance spectroscopy, diffusion MRI (dMRI) cerebral blood flow, cerebral vascular reactivity, and brain connectivity as measured by functional MRI (fMRI) and dMRI [9, 11, 12].

WMHs as a marker of WM damage are common across all studies of SVD. WMHs are easily observed in FLAIR images and software programs are available for automatic segmentation of WMH, making it possible to quantify them and follow their changes longitudinally [19]. WMHs to some extent are present in all cases of SVD. The disadvantage

of WMHs as a biomarker is that it is not specific to SVD, because it can occur with normal aging without causing any cognitive decline. WMHs of presumed vascular origin affect the periventricular/deep cerebral WM, basal ganglia, and pons. There is some discussion whether WMHs in subcortical gray matter should be included. If subcortical WMHs are included then the recommendation is that it should be explicitly stated [16]. Studies from 1966 to 2009 have been reviewed with meta-analysis for the clinical importance of WMHs [20]. In 99 subjects with ages in the range of 75–89 years, the increase in WMHs was associated with decline in cognition, mobility, and increase in depressive symptoms [21]. There has been a large European multicenter Leukoaraiosis and Disability (LADIS) study with 639 Patients in the range of 65–84 years of age. The results of the LADIS study have been previously reviewed [22]. Subjects were selected in this study with WMH classified in the ranges of mild, moderate, and severe based on a revised Fazekas scale [23]. Subjects with highest severity of WMHs at baseline already had functional impairment as measured by a forty item Disability assessment for dementia. The same scale also showed declining performance with increased WMHs.

WMHs are a binary indicator of WM damage: they indicate which regions have changes, but neither provides information about possible damage in normal-appearing WM (NAWM) on FLAIR nor information of the severity of damage within the WMHs. This ambiguity has contributed to the search for newer MRI methods, such as diffusion imaging to better characterize WM damage [24, 25]. The LADIS group also evaluated the value of diffusion imaging in conjunction with WMHs [26]. Here we review the different ways dMRI can be used to probe WM integrity as related to SVD.

3. Diffusion MRI (dMRI) Methods in VCI

There have been several reviews of dMRI [27–31] and an excellent book by Callaghan [32]. Here we give a short summary to introduce the terminology and the methods used in dMRI. The reader is referred to the previous reviews for more detailed explanations. The most common diffusion imaging experiment is the pulsed gradient spin echo (PGSE) [33], which effectively consists of a bipolar gradient pulse for encoding random motion followed by a spin-echo echo planar imaging sequence. If the water motion can be described by a Gaussian process then the signal in a voxel is given by $S = S_0 e^{-bd}$, where b is an experimental parameter depending on the diffusion sensitizing gradients.

Isotropic diffusion occurs when there is equal diffusion in all directions. If a preferred direction of diffusion exists, such as diffusion in cylindrical tubes, then we have anisotropic diffusion. A Gaussian anisotropic diffusion is described by a diffusion tensor D (symmetric 3×3 matrix with 6 unknowns), and the dMRI signal at a voxel is given by $S = S_0 e^{-bn^T Dn}$, where n is a normal vector along the gradient direction [34]. The diffusion tensor imaging (DTI) is the most widely used diffusion experiment. It assumes Gaussian translational motion of water molecules which leads to mono-exponential signal decay. The typical parameters calculated from DTI are mean diffusivity (MD) and fractional anisotropy (FA), which is a number from 0 to 1, and is a measure of the difference in the diffusion along the

three directions. FA is equal to 0 for isotropic diffusion and 1 for anisotropic diffusion when the diffusion is only in one direction.

Figure 1 shows when the diffusion is Gaussian and non-Gaussian and when it is isotropic and anisotropic with examples of simple geometries. In geometries with restriction and barriers the diffusion within the restricted geometries is non-Gaussian (also called restricted diffusion) and the diffusion in water outside the restricted spaces is Gaussian (also called hindered diffusion). If no restrictions are present the diffusion is isotropic (also called as free water diffusion). The Gaussian diffusion can be described by a single exponential while non-Gaussian is not mono-exponential. Diffusion weighted imaging (DWI) gives a measure of mean diffusivity by making diffusion measurement in three orthogonal directions and taking the mean of the diffusion coefficient in the three directions. This is a short simple experiment and was the precursor to DTI. The DTI experiment is currently the most widely used diffusion experiment. It has been useful to characterize the microstructure based on anisotropic Gaussian diffusion.

Gray matter consists of neuronal cell bodies, dendrites, myelinated and unmyelinated axons, astrocytes and oligodendrocytes. White matter consists of bundles myelinated axons connecting gray matter regions. In a typical diffusion MRI voxel of the size $2mm^3$, the tissue properties can be inhomogeneous. Several approached have been studied to model the tissue heterogeneity and the signal decay not being adequately defined by a single exponential. One approach to model tissue heterogeneity has been with multiple-compartment models. The taxonomy of different diffusion models and their relative merits have been reviewed [35, 36]. IVIM [37] is a diffusion technique which measures the microvascular perfusion and parenchymal tissue properties with the use of a 2-compartment diffusion model [38]. Few studies employed IVIM in SVD subjects to investigate the microstructural integrity and perfusion simultaneously [39, 40]. Other multicompartment models were developed to explain the partial volume effects of the large diffusion voxel ($2mm^3$). This includes the two-compartment free-water model to include the presence of CSF or edema in a voxel [41], the multi-compartment CHARMED model [42] which has hindered and restricted diffusion, and the three compartment NODDI model [43] which includes a free-water compartment, a hindered diffusion compartment and a restricted diffusion compartment. An alternative method to model deviation from the single exponential signal decay is the method of diffusion kurtosis imaging (DKI) based on the cumulant expansion of the diffusion signal [44]. This takes into account the non-Gaussian nature of diffusion of water molecules [45]. While there are have been no studies reported in VCI related disorders using CHARMED or NODDI, there have been a few studies utilizing free-water and DKI in VCI subjects [46–48].

Diffusion based tractography is a separate analysis category [49], which use local information of the orientation distribution of the white matter tracts and connects adjacent voxels to map white matter tracts from one gray matter region to another. A structural connectivity matrix, connecting different brain regions, can be calculated from the orientation distribution function at each voxel. Parameters based on network analysis, such as network efficiency, strength, path length and density can be further used in group analysis.

4. Diffusion MRI Studies

We reviewed the literature on diffusion MRI for chronic WM disease studies up to July 2018 in PubMed. The search query, "(diffusion mri OR diffusion magnetic resonance imaging OR DTI OR DWI OR DKI OR IVIM) AND (VCI OR vascular cognitive impairment OR SVD OR cerebral small vessel disease OR Binswanger's disease OR SIVD OR subcortical ischemic vascular disease OR leukoaraiosis OR mixed dementia)" was searched in keywords, title and abstract. References were searched to include any relevant article that was missed in the online database search. A total of 55 journal articles were finally selected for review.

The review focuses on various aspects such as diffusion acquisition protocols, the models used for data analysis and nature of WM disease studied. Diffusion acquisition protocols varied from employing single b-value shell to multi-shell acquisitions to cover a range of b-values and gradient directions. Diffusion biomarkers depended on the diffusion model and the type of analysis used in the studies. As an example, studies involving DTI used MD and FA as the parameters and performed whole brain or region based statistical analysis to report on the significance of such biomarkers in detecting the disease. In this review, the relevant studies are compared and categorized based on these different analysis methods. The diffusion methods include DWI, DTI, advanced multi-compartment diffusion models, tractography analysis, and connectivity analysis. Diseases primarily include LA, VCI, SIVD and SVD. Moreover, the analyses done by prominent study cohorts (LADIS, RUN DMC and SCANS) aimed at exploring biomarkers for vascular cognitive impairment are reviewed. Categorizing the articles based on the diseases studied yields a majority of them belonging to SVD with totally 33 articles out of 55 and rest of them are, 16 in LA, 5 in VCI and 1 reporting SIVD. Similarly, the number of studies categorized based on diffusion methods varies from 31 in DTI, 12 in tractography, 7 in DWI and 5 using other advanced diffusion models. Most of the works belong to one of the study cohorts, LADIS, RUNDMC or SCANS where 12 reported by RUN DMC, 9 by SCANS group and 3 were LADIS.

4.1. Diffusion Weighted Imaging (DWI)

Earlier studies used trace/apparent diffusion coefficient (ADC) images calculated from DWI to characterize abnormal WM regions in vascular cognitive impairment. The studies reviewed [50–56] are summarized in Table 1. All the reports studied the LA subject group, except for [56], who studied the SVD group. Among the studies reviewed there are two longitudinal studies. The main analysis method consisted of calculating the mean ADC, the histogram peak height, or its mode over either the WM, the whole brain region excluding the CSF, or the normally appearing brain tissue.

The main observations in the cross-sectional studies [50, 53, 55] was of increased ADC values with WMHs severity. ADC measures were correlated with other VCI markers such as MRI visual rating scale, blood pressure, gait score, neuropsychological tests scores and magnetization transfer ratio (MTR) maps. Age, blood pressure and visual scores were positively correlated with mean ADC values in NAWM and WMHs [52]. On the other hand, MTR metrics, attention and motor function scores negatively correlated with ADC [52–54]. The significance of ADC was reported to outperform other markers in detection of WM

pathology. Longitudinal studies [51, 55] showed increased diffusion with progression of WMH severity. Correlations between changes in ADC values with changes in other markers such as gait score, neuropsychological tests scores and brain volume index were also reported in these studies. While gait and MMSE score did not significantly change between time points of disease progression [51], ADC correlated with decline in cognitive measures such as speed and motor control, executive functions, and memory tests scores [55]. The main advantage of the ADC measure was its potential to differentiate acute and chronic lesions in LA. Memory, intelligence, attention, and executive function cognitive scores were strongly correlated with ADC in LA subjects. Irrespective of these benefits of ADC, the limitation of DWI model to represent anisotropic diffusion in neuronal tissues lead to DTI model in later SVD studies.

4.2. Diffusion Tensor Imaging (DTI)

Thirty two DTI studies were included for this review [47, 57–86]. We grouped the studies based on cross-sectional or longitudinal analysis. Seven of these reports studied LA subjects and others studied subgroups such as SVD, VCI and SIVD. We separately grouped the studies based on cross-sectional or longitudinal analysis. Studies on LA were entirely cross-sectional [47, 57, 62] whereas studies related to VCI were predominantly longitudinal. Longitudinal studies [63, 67, 70, 78–81, 83–86] focused on characterizing the disease progression using DTI measures.

4.2.1. Cross-sectional DTI Studies—The characteristics of cross-sectional DTI studies in LA subjects are tabulated in Table 2 and those for other disease groups (SVD, SIVD, and VCI) are summarized in Table 3. Except for [61], which is based on whole brain histogram and VBA analysis, the other 6 studies did regional analysis of mean MD and FA calculated on NAWM and WMH. These studies demonstrated low FA and high MD values in WMHs and NAWM of LA subjects as compared to controls. Studies [59, 61] which employed MRI FLAIR or T1 weighted volumes computed total brain volume, WMH volume, and parenchymal volume as conventional MRI markers. These studies showed that DTI had better correlation with cognitive scores than WMHs or other regional brain volumes.

Some studies used other MRI biomarkers, such as magnetic resonance spectroscopy [60] and cerebral blood flow (CBF) measured by arterial spin labelling (ASL) [47]. MRS markers included N-acetyl aspartate (NAA), total cholines (Cho), combined glutamate and glutamine (Glx) and myo-inositol (mI). CBF was calculated in WMH, normal appearing WM (NAWM) and cortex. These measures were correlated with cognitive scores. Among these other MRI markers DTI showed the strongest correlation with cognitive scores. Table 2 describes the group analysis and correlation results of each study. The characteristics of cross-sectional DTI studies VCI, SIVD and SVD (Table 3) were similar to the LA subjects. Regional and histogram based analysis were used. Parameters such as median, histogram peal height and histogram mode were computed. The decreased anisotropy and increased diffusion were clinically correlated to the axonal loss, demyelination and gliosis observed in VCI subjects. The correlation between MD and FA were consistent with cognitive decline

whereas correlations for other MRI markers were weaker. Despite these advantages, the pathogenesis underlying DTI changes is not clearly understood.

4.2.2. Longitudinal DTI Studies—Longitudinal studies are important because they answer questions related to disease progression and identify early markers of the disease. The results from various longitudinal studies ranging from 1 to 8 years of follow-up are reported in Tables 4–6. Two longitudinal studies from individual groups are reported in Table 4 [63, 67]. DTI whole brain histogram features showed changes towards increased MD and decreased FA in a span of 1 year period [63], whereas significant changes in DTI over thalamus and putamen correlating with WMHs accrual over a period of 4 years shown in another study [67]. Two other studies have reported on the significance of a single DTI measure calculated from DTI image [70, 85]. These include the peak width of skeletonized MD (PSMD) and a novel DTI segmentation angular measure. These markers characterized the SVD related brain changes in both cross-sectional and longitudinal studies. RUN DMC (Radboud University Nijmegen Diffusion tensor and Magnetic resonance imaging Cohort) study [87] summarized in Table 5 and SCANS (St George's Cognition and Neuroimaging in Stroke) study [83] summarized in Table 6 were the 2 large cohort studies with 8 and 3 years follow-up period respectively reporting SVD related biomarkers.

RUN DMC group has published results both on cross-sectional and longitudinal analysis with 8 years follow-up period. DTI, MRI, neuropsychological tests scores and dementia risk score were collected as part of this study. Nearly 500 SVD subjects were included with 8 years follow-up scans and the diffusion data was collected using a 1.5 T Siemens scanner with b-value of 900 s/mm^2 in 30 gradient directions. Cross-sectional studies [73–77, 88] showed DTI outperforming conventional MRI markers such as WMH volume, hippocampal volume and number of lacunar infarcts. Moreover, DTI measures were strongly correlated with hippocampal integrity in diseased subjects. The longitudinal analysis demonstrated DTI changes with disease progression significant correlations with risk of dementia and mortality risk. DTI changes were observed in NAWM and hippocampus which makes DTI, a good predictor of conversion to dementia and risk of death. Unlike RUN DMC, SCANS reports were predominantly longitudinal (Table 6), and aimed at analyzing the histogram features and estimating sample size required for those features. The study cohort includes nearly 100 SVD subjects with 3 year follow-up scans collected using 1.5 T GE scanner with b-value of 1000 s/mm^2 in 25 gradient directions. One cross-sectional study [82] detailed on the significance of histogram derived features from entire DTI maps such as MD, FA, AxD and RD. The diffusion observations in NAWM correlated with cognitive decline. On the other hand, longitudinal analyses [83–86] proved histogram peak height of MD to be better than any other measure in predicting disease progression with a smaller sample size estimate.

4.2.3. DTI measures in VCI Subjects—Mean values of MD and FA in NAWM collected from the reviewed studies are summarized in Table 7. MD is higher in patients as compared to healthy controls. Among the patients, MD is least in AD and highest in SIVD. FA shows an inverse trend to that of MD across the subgroups. Interestingly, the MD for NAWM is higher in patients than for HCs, indicating that white matter damage is seen in NAWM, which is classified as normal by FLAIR.

4.3. Studies using Other Diffusion Models

DKI can model non-Gaussian diffusion and various DKI metrics such as mean kurtosis, axial and radial kurtosis (in addition to DTI metrics) were helpful in disease diagnosis. Two DKI studies [46, 47] showed increased sensitivity of DKI measures which could differentiate NAWM between mild and severe LA subjects and better correlated with cognitive decline as compared to cerebral blood flow. The IVIM model simultaneously offers microstructural and microvascular perfusion of WM and GM. SVD studies using IVIM [39, 40] showed increased parenchymal diffusivity and decreased perfusion in SVD patients, with cognitive decline correlations in WM lesions. A recent study [48] published the significance of free water diffusion model in characterizing SVD. This model separates the free water fraction from the anisotropic diffusion in WM based on a two compartment model. Increased extracellular fluid was suggested to be the main cause behind diffusion alterations in SVD rather than degeneration of WM tracts. More studies in future are required with advanced models to resolve the pathogenesis underlying diffusion MRI changes in VCI.

4.4. Structural Connectivity

Structural connectivity in brain denotes the connectivity between brain regions established by tracts running between any 2 regions. Tracts are generated by fiber tracking algorithms which could be deterministic or probabilistic [28, 89]. Measures extracted from these tracts are of significance in differentiating disease from normal tissues. Extending this, network based connectivity analysis involve incorporating network measurements from connectivity matrices [90]. The relevant studies included in this review are summarized in Table 8. Most of the studies performed tractography based on deterministic fiber tracking [91, 92] except [93, 94] where probabilistic tracking based on constrained spherical deconvolution (CSD) model [95] was followed. Network measures such as network efficiency and connectivity strength were used widely except [94, 96, 97] where the DTI values were analyzed on WM tracts.

All network measures indicated network disruption in tracts passing through NAWM and WMHs regions. Longitudinal analysis showed network disruption in dementia subjects as compared non-dementia in the follow-up period. Tractography analysis is attractive as compared to regional or histogram methods because it potentially identifies tracts related to specific cognitive decline. In future, more studies are anticipated with advanced CSD model based probabilistic tractography analysis [98]. Moreover, fixel based analysis [99] which computes metrics on more than one fiber population present within a voxel is potentially another significant method for predictions in SVD.

5. Conclusion

DTI with parameters MD and FA is currently the most widely used diffusion method to study SVD subjects. Several groups have been studying the relationship between MD, FA and the NAWM in the FLAIR image. The general trend is that in damaged white matter MD increases and FA goes down because of breakdown of axon walls and fluid accumulation. These results collected across various studies shows that even the NAWM appears to be

damaged in the diffusion image. Newer diffusion imaging methods are being developed to probe the microstructure more closely. These methods include building biophysical models so that tissue structure can be parsimoniously defined by fewer parameters that reflect tissue properties. The NODDI model discussed earlier is in this class of methods. More importantly alternative methods of data acquisitions are also being developed which employ more complex diffusion encoding (other than bipolar gradients of the PGSE experiment) to decode the tissue heterogeneity within a voxel. These methods are sensitive to the variability of the mean diffusivity within a voxel (size variance) and to the variability of the fiber orientation within a voxel (micro anisotropy) [108].

Abbreviations

AD	Alzheimer's disease
CADASIL	Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy
HC	Healthy Controls
MCI	Mild cognitive impairment
MS	Multiple sclerosis
SIVD	Subcortical ischemic vascular disease
SVD	Cerebral small vessel disease
VCI	Vascular cognitive impairment
VCID	Vascular cognitive impairment and dementia
b	b-value in s/mm2
D	Gradient directions
T	Tesla
dMRI	Diffusion MRI
DTI	Diffusion Tensor Imaging
DWI	Diffusion weighted MRI
FLAIR	Fluid Attenuated Inversion Recovery
fMRI	Functional MRI
IVIM	Intravoxel incoherent motion imaging
MRS	Magnetic resonance spectroscopy
ADC	Apparent diffusion coefficient
CBF	Cerebral blood flow

FA	Fractional Anisotropy
FS	Fazekas Scale
FW	Freewater fraction
GM	Gray Matter
MD	Mean diffusivity
MTR	Magnetization transfer ratio
NAA	N-acetyl aspartate
NAWM	Normal appearing White Matter
WM	White Matter
WMH	WM Hyperintensity
VBM	Voxel based morphometry
BP	Blood pressure
CS	Cognitive Score
FABS	Total score of Frontal Assessment Battery
GS	Gait Score
MMSE	Mini mental state examination
VSS	Visual scale score
WCST	Wisconsin Card Sorting Test

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Highlights

- We review diffusion MRI studies in chronic white matter diseases.
- DTI with parameters MD and FA is currently the most widely used diffusion method to study SVD subjects.
- In damaged white matter MD increases and FA goes down because of breakdown of axon walls and fluid accumulation.
- Various studies reveal that even the NAWM appears to be damaged in the diffusion images.
- Future studies should be aimed at multi-compartment and higher order diffusion models.

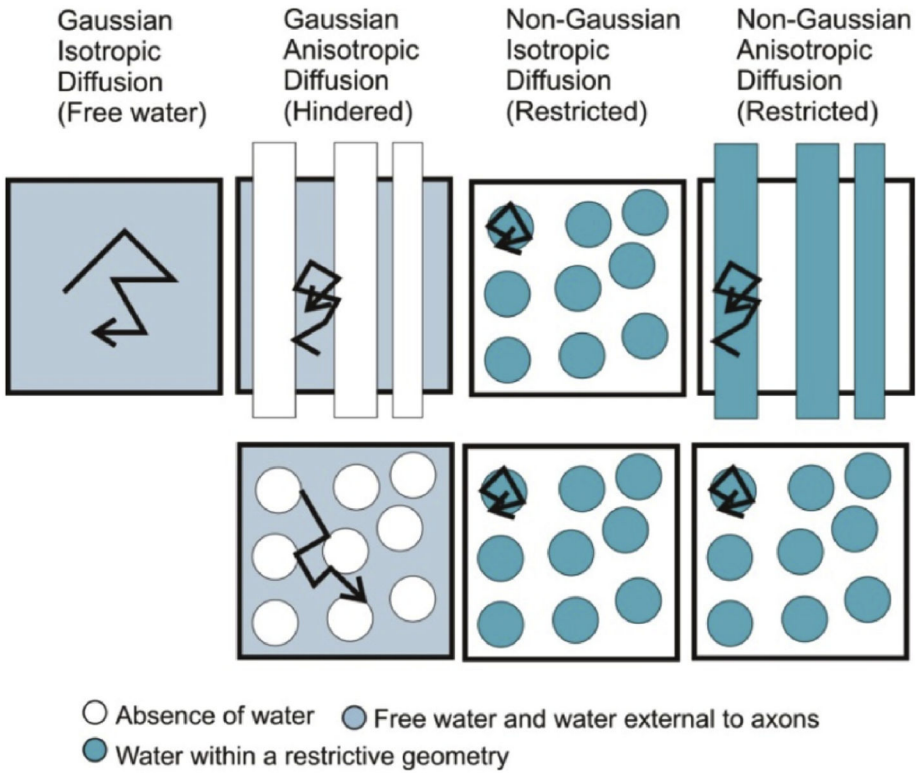

Figure 1.

The figure shows examples when the diffusion is Gaussian and non-Gaussian and when it is isotropic and anisotropic. Isotropic diffusion occurs in fluids without barriers or spherically symmetric barriers. Anisotropic diffusion occurs when there is a preferential direction for diffusion. In a geometry with a bundle of cylindrical tubes, diffusion in the fluid outside the tubes and the diffusion of water in the tubes is both anisotropic because the diffusion along the length of the tubes is greater because it is unrestricted as compared to the diffusion perpendicular to the tubes axis. The diffusion in the space outside the tubes can be approximated by Gaussian diffusion while the diffusion within the tubes is bounded by the tube walls and is non-Gaussian. The diffusion in the space external to the tubes is also hindered and the diffusion within the tubes restricted diffusion.

Table 1:

Characteristics of DWI Studies

Study/Subject	dMRI Protocol	Analysis	Findings
Helenius et al., 2001 [50] **LA=85, HC=22, IS=10**	Siemens 1.5T b=1000, D=3	Cross-sectional Regional	High ADC in WMHs and NAWM of severe LA than mild LA
Viana-Baptista et al., 2008 [52] **LA=29**	GE 1.5T b=1000, D=6	Cross- sectional Regional	Positive correlation of ADC with Age, BP, VSS and negative correlation with attention
Ropele et al., 2009 [53] **LA=340**	1.5T b=900–1000, D=3	Cross- sectional Histogram	ADC and not magnetization transfer ratio was related to WMH severity
Viana-Baptista et al., 2011 [54] **LA=29**	GE 1.5T b=1000, D=6	Cross- sectional Regional	Significant negative correlations between ADC and motor function
Oztoprak et al., 2015 [56] **SVD=50, MS=35, HC=85**	Siemens 1.5T b=1000, D=3	Cross- sectional Regional	High ADC in thalamus of S VD subjects than in MS and HC
Mascalchi et al., 2002 [51] **LA=10**	Philips 1.5T b=1000, D=3	Longitudinal Histogram	ADC increases, brain volume index decreases with disease progression; No change in GS, MMSE
Jokinen et al., 2013 [55] **LA=340**	1.5T b=900–1000, D=3	Longitudinal Histogram	ADC correlates with cognitive decline and disease progression.

Table 2.

Characteristics of Cross-sectional DTI studies in LA Subjects

Study/Subject	dMRI Protocol	Analysis	Findings
Jones et al., 1998 [57] **LA=9, HC=10**	GE 1.5T b=0-614 D=7	Regional	Low FA and High MD in NAWM of LA subjects as compared to HC
O'Sullivan et al., 2001 [58] **LA=30, HC=17**	GE 1.5T	Regional	Low FA and High MD in LA than in HC; MMSE and WCST correlated with MD and FA
O'Sullivan et al., 2004 [59] **LA=36, HC=19**	GE 1.5T	Regional	MD and FA differences between LA and HC in WMHs and in NAWM; No correlations between WMH volume and CS but significant correlations between FA and MD of NAWM and CS
Nitkunan et al., 2006 [60] **LA=25**	GE 1.5T b=1000 D=12	Regional	Positive correlation between mean NAA and FA, and negative correlation with MD; Positive correlation between WMH volume and MD, and negative correlation with FA
Nave et al., 2007 [61] **LA=36**	GE 1.5T b=1000 D=32	VBA, Histogram	No correlations between GM/WM volume and CS Significant correlations between MD and FA with CS
Wang et al., 2017 [62] **LA=42, HC=42**	Siemens 3T b=1000 D=20	Regional	MD and FA differences between LA and HC in WMHs and in NAWM; FA positively correlated with CS but no correlation with MD
Zhong et al., 2017 [47] **LA=75**	GE 3T b=1000 D=30	Regional	MD and FA are significantly correlated with CS and their correlation is higher than the correlation of CBF with CS

Table 3.

Characteristics of Cross-sectional studies reporting DTI findings in SVD, SIVD and VCID

Study/Subject	dMRI Protocol	Analysis	Findings
Nitkunan et al., 2008 [64] **SVD=29, HT=63, NT=42**	GE 1.5T b=1000	Regional	High WMH volume in SVD; Higher MD, lower FA and lower NAA with disease progression;
Zhou et al., 2008 [65] **VCI=19, PS=19, HC=19**	Philips 3T b=800 D=15	Histogram	Lower FA in VCI and PS than HC; MMSE correlated with FA in VCI, whereas MMSE correlated with MD in PS and HC
Kim et al., 2011 [66] **MCI=27, Dementia=34**	GE 3T b=600 D=45	VBM	MD and FA are significantly correlated with cognitive and motor deficits
Huang et al., 2014 [68] **SVD=12, HC=6**	GE 1.5T b=1000	Regional	Significant difference between SVD and HC for MD but not for NAA, and weak but not significant differences in FA
Thong et al., 2014 [69] **Mild VCI=25, Moderately severe VCI=30, AD=20 HC=25**	Siemens 3T b=1150 D=61	VBA, Regional	Thinner cortex and lower volumes in all disease groups as compared to HC; Higher MD and lower FA in moderately severe VCI and AD than in HC; Only higher MD in mild VCI than HC;
Croall et al., 2017 [71] **SVD=199**	3T b=1000 D=32	Histogram	Significant correlations between DTI and number of lacunar infarcts with CS, but none between WMH volume and CS
Tu et al., 2017 [72] **SIVD=35, AD=40, HC=33**	GE 3T b=1000 D=20	Regional	Higher Fazekas scale and MD and lower FA and FABS in SIVD than in AD

Table 4.

Characteristics of longitudinal studies reporting DTI findings

Study/Subject	dMRI Protocol	Analysis	Findings
Nitkunan et al., 2008 [63] **LA, at baseline=35, LA at one year=27**	GE 1.5T b=1000 D=12	Histogram	Higher MD and lower FA, but no changes in WMH volume, brain volume, and CS between time points
Cavallari et al., 2014 [67] **SVD=56**	Siemens 3T b=1000 D=12	Regional	Baseline: Thalamus and putamen MD correlated with WMH volume; Follow-up: Thalamus FA correlated with annual WMH accrual rate over 4 years

Table 5:

Characteristics of RUN DMC studies

Study	Analysis	Findings
Gons et al., 2010 [73]	Cross- sectional Regional	BP correlated with WMHs volume; High BP correlated with low FA and high MD; Lower FA and higher MD in HT than in NT
van Norden et al., 2012 [74]	Cross- sectional Regional	DTI correlated with CS in mild, moderate and severe WMHs; DTI had limited additional value as compared to WMHs volume with respect to correlations with cognitive decline
van der Hoist et al., 2013 [77]	Cross- sectional Regional, TBSS	DTI correlated with CS and hippocampal integrity; Higher MD associated with 5 year dementia risk
Tuladhar et al., 2015 [88]	Cross- sectional Regional, TBSS	DTI of genu and splenium correlated with CS; DTI of various WM tracts related to CS
van Uden Hoist et al., 2015 [78]	Longitudinal Regional	No significant relation between DTI and CS decline after adjusting for confounders; Higher MD associated with 5 year dementia risk
van Leijsen et al., 2018 [81]	Longitudinal Regional	WM damage can be detected by DTI before the appearance of WMH lesions.

Table 6:

Characteristics of studies belonging to SCANS study

Study	Analysis	Findings
Lawrence et al., 2013 [82]	Cross-sectional Histogram	DTI and number of lacunar infarcts correlated with CS decline; DTI suggested ischemic demyelination in SVD
Benjamin et al., 2016 [83]	Longitudinal Histogram	DTI and WMH volume had greater significance in predicting disease progression than CS
Zeestraten et al., 2016 [84]	Longitudinal Histogram	Histogram peak height of MD was the most sensitive marker for disease progression among all other DTI metrics
Williams et al., 2017 [85]	Longitudinal Histogram	A novel DTI segmentation method predicted cognitive decline over a 3 year period
Zeestraten et al., 2017 [86]	Longitudinal Regional	DTI markers and WMH volume correlated significantly with CS decline and predicted dementia over 3 years.

Table 7.

Mean values of MD and FA in NAWM reported for healthy controls (HC), Leukoaraiosis (LA), Alzheimer's disease (AD), cerebral small vessel disease (SVD) and subcortical ischemic vascular disease (SIVD) collated from reviewed papers

Subject Group	HC	LA	AD	SVD	SIVD
Mean MD	0.8±0.05	0.87±.04	0.82±0.17	0.92±0.12	1.12±0.4
Mean FA	0.4±0.07	0.34±0.06	0.39±0.09	0.31±0.06	0.32±12

Table 8:

Characteristics of studies using tractography and diffusion based connectivity analysis

Study/Subjects	Diffusion Protocol	Analysis	Conclusions
Correia et al., 2008 [100] **VCI=14, HC = 18**	Siemens 1.5T DTI b=1000, D=12	Cross-sectional Connectivity Network Analysis	Significant correlations between network measures and cognitive scores
Lawrence et al., 2014 [101] **LA = 115, HC=50**	GE 1.5T DTI b=1000, D=25	Cross-sectional Connectivity Histograms	Reduced network connectivity in SVD. Network measures have stronger correlation with cognitive scores than with WMH volume
Kim et al., 2015 [102] **VCI = 232**	Phillips 3T DTI b=1000, D=45	Cross-sectional Connectivity Whole Brain	Network segregation correlated with cognitive scores and WMHV
Reijmer et al., 2016 [93] **VCI = 232**	Siemens 3T b=700	Cross-sectional Connectivity Whole Brain	FA correlated with cognitive scores in central brain regions
Tuladhar et al., 2016 [103] **SVD = 436**	Siemens 1.5T DTI b=900, D=30	Cross-sectional Connectivity Whole Brain	WMH volume and MD of WM correlates with cognitive scores
Tuladhar et al., 2016 [104] **SVD = 436**	Siemens 1.5T DTI b=900, D=30	Longitudinal Connectivity Whole Brain	Network efficiency predicts dementia
Metoki et al., 2017 [96] **SVD = 106**	GE 1.5T DTI b=1000, D=25	Cross-sectional Cingulum Uncinate fasciculus	Lower memory scores in SVD than HC MD correlated with memory scores FA only correlated with working memory
Lawrence et al., 2018 [105] **SVD=26, HC=19**	Siemens 3T DTI b=1000, D=63	Cross-sectional Connectivity Whole Brain ROIs	Lower network measures in SVD than HC Similar fMRI network measures in SVD andHC
Biesbroek et al., 2018 [94] **VBI=159**	Phillips 3T DTI b=1200, D=45	Cross-sectional Connectivity Whole Brain ROIs	Specific white matter tracts are strongly correlated with specific cognitive scores
D'Souza et al., 2018 [97] **SVD=30**	Siemens 3T DTI b=1000, D=30	Cross-sectional Connectivity Whole Brain ROIs	MD and FA are correlated with cognitive scores and no correlation with WMH volume
Lawrence et al., 2018 [106] **SVD=97**	GE 3T DTI b=1000, D=30	Longitudinal Network Connectivity Histogram	Network global efficiency during follow up correlated with increased dementia
Lisiecka-Ford et al., 2018 [107] **SVD=114**	GE 3T DTI b=1000, D=30	Cross-sectional Connectivity Whole Brain ROIs	Network efficiency of reward network negatively correlated with apathy scores.