International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Website: https://ijmpr.in/

Review Article

Beyond ADC: Advanced Diffusion-Weighted MRI Techniques and Their Clinical Applications in Neurology

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Received: 07-02-2026
Accepted: 12-03-2026
Published: 31-03-2026

ABSTRACT

Diffusion-weighted imaging (DWI) has become a cornerstone of neuroimaging by enabling non-invasive assessment of tissue microstructure through the measurement of water molecule motion. The apparent diffusion coefficient (ADC), derived from conventional mono-exponential modeling, has demonstrated significant clinical utility, particularly in acute ischemic stroke and tumor evaluation. However, its limited specificity and inability to capture the complex, non-Gaussian behavior of water diffusion in biological tissues have driven the development of advanced diffusion MRI techniques.

This review provides a comprehensive overview of diffusion MRI methods beyond ADC, including diffusion tensor imaging (DTI), diffusion kurtosis imaging (DKI), intravoxel incoherent motion (IVIM), and multi-compartment models such as neurite orientation dispersion and density imaging (NODDI). These techniques offer improved characterization of tissue microstructure by incorporating directional diffusion, non-Gaussian signal behavior, and compartmental modeling. Advances in acquisition strategies, including multi-shell imaging and high b-value diffusion, along with artificial intelligence-based reconstruction and analysis, have further enhanced the capabilities and clinical feasibility of diffusion MRI.

The clinical applications of advanced diffusion MRI in neurology are discussed, including its role in acute stroke, brain tumors, demyelinating diseases, neurodegenerative disorders, epilepsy, and developmental conditions. Emerging techniques such as whole-brain IVIM, ultra-high b-value imaging, and diffusion fingerprinting are also highlighted. Despite these advancements, challenges related to standardization, reproducibility, and biomarker validation remain significant barriers to widespread clinical adoption.

Future directions emphasize the need for harmonized acquisition protocols, multicenter validation, integration with complementary imaging modalities, and the incorporation of artificial intelligence to improve robustness and efficiency. In conclusion, advanced diffusion MRI holds substantial promise as a quantitative imaging biomarker, with the potential to significantly enhance the diagnosis, monitoring, and understanding of neurological diseases.

Keywords: *Diffusion Magnetic Resonance Imaging; Diffusion Tensor Imaging; Diffusion Kurtosis Imaging; Neurite Orientation Dispersion and Density Imaging; Intravoxel Incoherent Motion; Brain Diseases; Neuroimaging; Biomarkers.*

INTRODUCTION

Diffusion-weighted imaging (DWI) has become an indispensable component of modern neuroimaging, providing unique insights into the microscopic movement of water molecules within biological tissues. The fundamental principle of diffusion MRI is based on the random Brownian motion of water molecules, which is influenced by the underlying cellular architecture, including cell density, membrane integrity, and extracellular space. By applying diffusion-sensitizing gradients, DWI enables indirect characterization of tissue microstructure, making it particularly valuable in neurological disorders where microstructural alterations often precede macroscopic changes (Fig. 1). The apparent diffusion coefficient (ADC), derived from conventional mono-exponential modeling of diffusion signal decay, has been widely used as a quantitative parameter to assess tissue diffusivity in clinical practice, particularly in acute ischemic stroke, tumors, and infections [1].

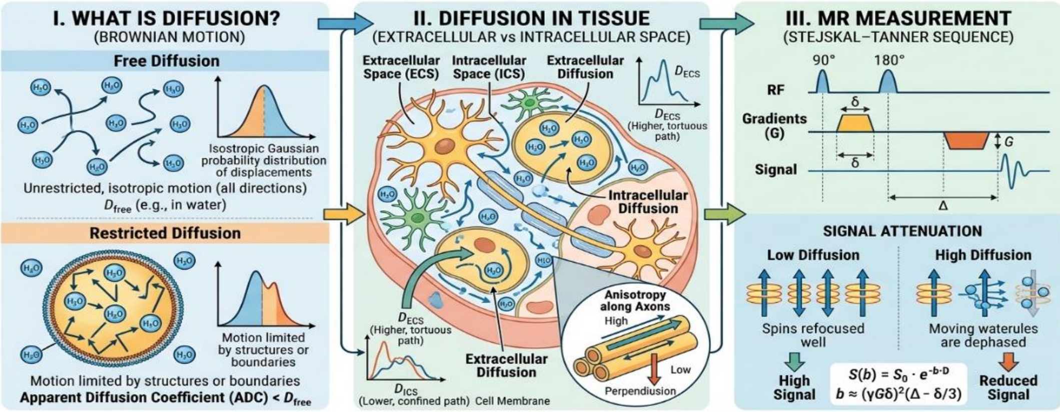

Figure 1. Basic principles of diffusion-weighted MRI.

(I) Free (Gaussian) diffusion of water molecules. (II) Restricted diffusion in biological tissues. (III) Diffusion encoding using gradient pulses and resulting signal attenuation.

Despite its widespread clinical utility, ADC has inherent limitations that restrict its ability to fully capture the complexity of biological tissues. The mono-exponential model assumes Gaussian diffusion behavior, which does not adequately reflect the heterogeneous and restricted diffusion environment of the brain (Fig. 2). In reality, water diffusion in neural tissue is often non-Gaussian due to barriers such as cell membranes, myelin sheaths, and intracellular organelles. As a result, ADC provides a simplified and sometimes non-specific representation of tissue microstructure, limiting its diagnostic specificity in conditions such as tumor characterization, neurodegeneration, and demyelinating diseases [2,3]. Furthermore, ADC is unable to disentangle different microstructural components, such as neurite density, orientation dispersion, or microvascular perfusion, leading to potential overlap between pathological entities.

To overcome these limitations, advanced diffusion MRI techniques have been developed to provide a more comprehensive characterization of tissue microstructure (Fig. 3). Diffusion tensor imaging (DTI) extends conventional DWI by incorporating directional information, enabling assessment of white matter integrity through parameters such as fractional anisotropy and mean diffusivity. However, DTI still relies on the Gaussian diffusion assumption and is limited in regions with complex fiber architecture. Diffusion kurtosis imaging (DKI) addresses this limitation by quantifying non-Gaussian diffusion behavior, thereby providing additional information about tissue complexity and heterogeneity [3,4]. Similarly, intravoxel incoherent motion (IVIM) imaging enables the separation of diffusion and perfusion components, offering insights into microvascular characteristics without the need for exogenous contrast agents [5,6].

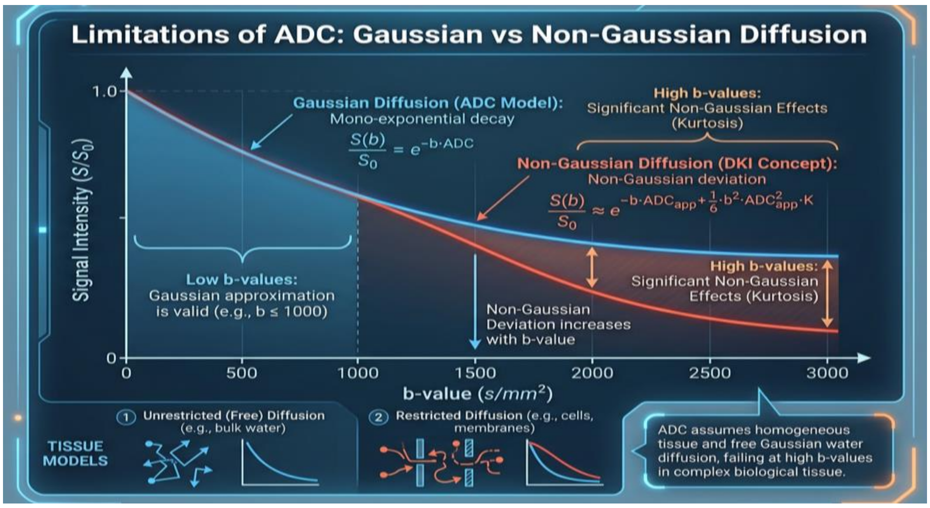

Figure 2. Gaussian vs non-Gaussian diffusion behavior.

ADC assumes mono-exponential (Gaussian) signal decay at low b-values, while high b-values reveal non-Gaussian behavior better captured by DKI.

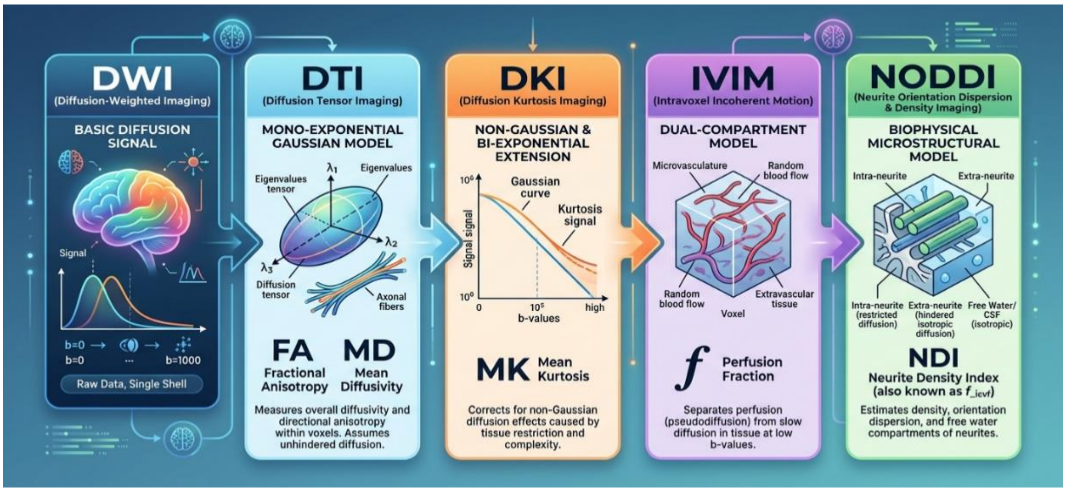

Figure 3. Overview of advanced diffusion MRI models beyond ADC.

Overview of diffusion models including DTI, DKI, IVIM, and NODDI with key parameters and microstructural interpretation.

More recently, multi-compartment diffusion models have been introduced to estimate specific microstructural features. Among these, neurite orientation dispersion and density imaging (NODDI) allows quantification of neurite density and orientation dispersion, improving sensitivity to subtle pathological changes in neurological and psychiatric disorders [7,8]. Advances in acquisition strategies, including multi-shell diffusion imaging and high to ultra-high b-value techniques, have further enhanced the sensitivity of diffusion MRI to restricted diffusion and microstructural alterations (Fig. 4) [9,10]. In parallel, the integration of artificial intelligence (AI) into diffusion MRI has enabled accelerated acquisition, improved image quality through denoising and reconstruction, and more robust estimation of diffusion parameters, thereby facilitating clinical translation (Fig. 5) [11-13].

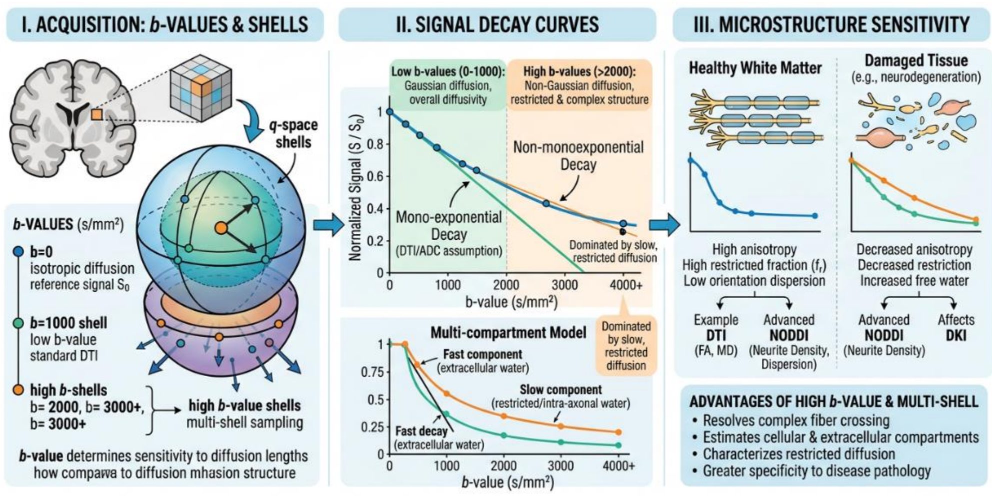

Figure 4. Multi-shell acquisition and high b-value diffusion imaging.

(I) Multi-shell imaging enables advanced models (NODDI, DKI). (II) Increased sensitivity to restricted diffusion at higher b-values.

These methodological developments have significantly expanded the clinical applications of diffusion MRI in neurology. Advanced diffusion techniques are increasingly used for improved characterization of acute ischemic stroke, brain tumors, demyelinating diseases such as multiple sclerosis, and neurodegenerative disorders. Quantitative diffusion metrics have demonstrated potential as imaging biomarkers for disease diagnosis, prognosis, and treatment monitoring, although challenges related to standardization, reproducibility, and multicenter validation remain [14-16].

In this context, the present review aims to provide a comprehensive overview of advanced diffusion-weighted MRI techniques beyond ADC, focusing on their technical principles, acquisition strategies, and clinical applications in neurology. Particular emphasis is placed on emerging diffusion models, including DKI, IVIM, and multi-compartment approaches such as NODDI, as well as recent advances in high b-value imaging and AI-driven reconstruction methods. Additionally, this review highlights current limitations, challenges in clinical implementation, and future directions toward the integration of diffusion MRI as a quantitative biomarker in precision neurology.

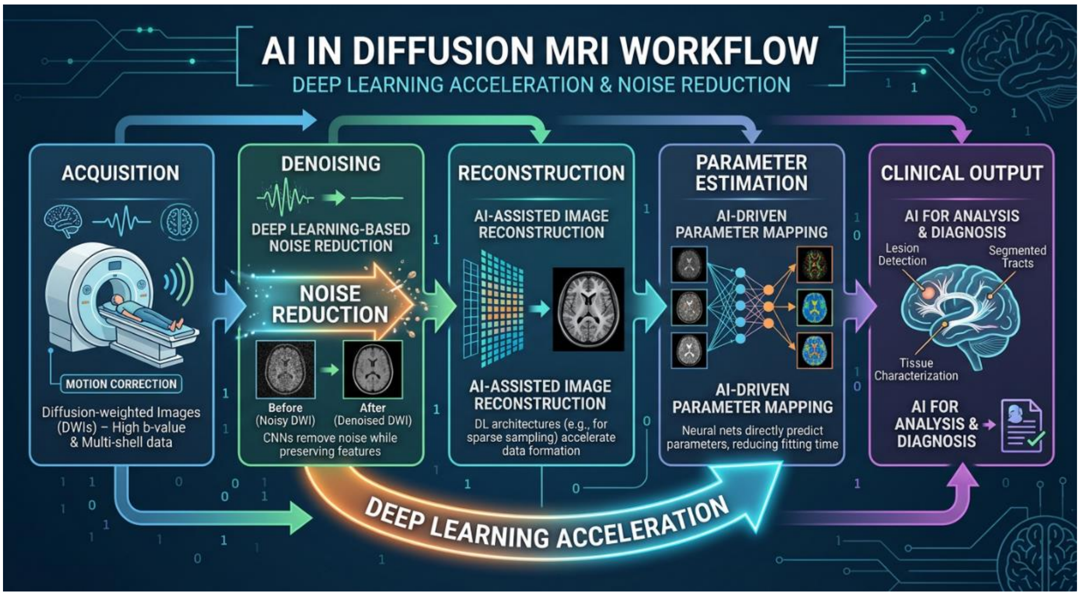

Figure 5. AI in diffusion MRI workflow.

AI-based pipeline for denoising, reconstruction, parameter estimation, and clinical interpretation.

FUNDAMENTALS OF DIFFUSION MRI

Diffusion physics and the b-value concept

Diffusion MRI is based on the measurement of the random Brownian motion of water molecules within biological tissues, which is influenced by the underlying microstructural environment. In the brain, water diffusion is not free but is restricted and hindered by cellular membranes, myelin sheaths, and intracellular organelles. These interactions result in complex diffusion behavior that reflects tissue architecture at the microscopic level. Diffusion-weighted imaging (DWI) sensitizes the MRI signal to this motion through the application of diffusion-encoding gradients, enabling indirect assessment of tissue microstructure [1,17].

The degree of diffusion weighting is quantified by the b-value, a parameter determined by the strength, duration, and timing of the applied diffusion gradients. Increasing the b-value enhances sensitivity to slower and more restricted diffusion components but also leads to a reduction in signal-to-noise ratio (SNR). Conventional clinical DWI typically employs b-values in the range of 0–1000 s/mm², which are sufficient for detecting acute ischemic stroke. However, higher b-values (e.g., ≥2000 s/mm²) have been increasingly utilized to probe non-Gaussian diffusion behavior and improve sensitivity to microstructural heterogeneity, particularly in tumors and neurodegenerative diseases [9].

The signal attenuation in DWI is commonly modeled using a mono-exponential decay function to derive the apparent diffusion coefficient (ADC). While this approach is computationally simple and clinically practical, it assumes Gaussian diffusion and therefore does not fully capture the complexity of biological tissues. Advanced diffusion models extend this framework by incorporating non-Gaussian effects, multi-compartmental behavior, or perfusion-related signal contributions, providing a more comprehensive representation of tissue microstructure [2,6].

Pulse sequences for diffusion-weighted imaging

The acquisition of diffusion-weighted images relies on specialized MRI pulse sequences that incorporate diffusion-sensitizing gradients. The most widely used technique in clinical practice is single-shot echo-planar imaging (ss-EPI), which enables rapid image acquisition within a single excitation. This approach minimizes motion sensitivity and allows whole-brain coverage in a short time, making it particularly suitable for acute clinical settings such as stroke imaging. However, ss-EPI is highly susceptible to geometric distortions and susceptibility artifacts due to its long echo train and low bandwidth in the phase-encoding direction [1].

To address these limitations, alternative acquisition strategies have been developed. Readout-segmented echo-planar imaging (rs-EPI) divides the k-space acquisition into multiple segments, thereby reducing echo spacing and minimizing susceptibility-induced distortions. This technique improves spatial resolution and image quality, particularly in regions prone to artifacts such as the skull base and temporal lobes. However, rs-EPI requires longer acquisition times and is more sensitive to motion between segments, necessitating robust motion correction strategies [15].

Multi-shot diffusion imaging further enhances spatial resolution and reduces distortions by acquiring k-space data over multiple excitations. This approach allows for shorter echo spacing and improved image fidelity but introduces phase inconsistencies between shots, which can lead to artifacts if not properly corrected. Advanced reconstruction techniques, including navigator-based correction and parallel imaging, have been developed to mitigate these issues and enable reliable multi-shot diffusion imaging [15].

In addition to these approaches, hybrid techniques combining segmented acquisition and parallel imaging have been introduced to balance acquisition speed, image quality, and artifact reduction. The choice of pulse sequence depends on the clinical application, with ss-EPI remaining the standard for routine imaging, while rs-EPI and multi-shot techniques are increasingly used in research and advanced clinical protocols where higher image quality is required [1,15].

Image artifacts and quality factors

Despite its clinical utility, diffusion MRI is inherently sensitive to a variety of artifacts and technical limitations that can affect image quality and quantitative accuracy. One of the most prominent challenges is geometric distortion, which arises from magnetic field inhomogeneities and susceptibility differences, particularly at air–tissue interfaces such as the sinuses and skull base. These distortions are exacerbated in echo-planar imaging due to its low bandwidth in the phase-encoding direction and can lead to spatial misregistration of diffusion images [1].

Motion artifacts represent another significant challenge in diffusion MRI. Patient motion, including bulk head movement and physiological motion such as cardiac pulsation and respiration, can introduce phase errors and signal inconsistencies, particularly in multi-shot acquisitions. These effects can degrade image quality and compromise the accuracy of diffusion parameter estimation. Various motion correction techniques, including prospective motion correction and post-processing algorithms such as eddy current correction and image registration, are commonly employed to mitigate these effects [15]. Eddy currents, induced by rapidly switching diffusion gradients, can cause image distortions and spatial shifts, further affecting the accuracy of diffusion measurements. Modern MRI systems incorporate gradient pre-emphasis and correction algorithms to reduce eddy current effects, although residual distortions may still be present and require post-processing correction [15].

The signal-to-noise ratio (SNR) is a critical determinant of diffusion MRI quality and reliability. Higher b-values, while providing increased sensitivity to restricted diffusion, result in reduced signal intensity and lower SNR. This trade-off necessitates careful optimization of acquisition parameters, including the number of signal averages, voxel size, and diffusion directions. Advances in hardware, such as high-field MRI systems and stronger gradient coils, as well as software developments including denoising algorithms and parallel imaging, have contributed to improvements in SNR and overall image quality [9,18].

Recent developments in artificial intelligence and advanced reconstruction techniques have further enhanced diffusion MRI by enabling improved denoising, artifact reduction, and accelerated acquisition. Deep learning-based methods have shown promise in improving image quality while preserving quantitative accuracy, thereby facilitating the clinical implementation of advanced diffusion imaging protocols [11,12,18].

Quantitative Diffusion Models

Diffusion MRI has evolved substantially beyond the conventional apparent diffusion coefficient (ADC), with the development of quantitative models that aim to better characterize the complex microstructural environment of brain tissue. These models differ in their underlying assumptions, acquisition requirements, and biological interpretability. This section provides an overview of major diffusion models, including diffusion tensor imaging (DTI), diffusion kurtosis imaging (DKI), intravoxel incoherent motion (IVIM), and multi-compartment approaches such as neurite orientation dispersion and density imaging (NODDI), as well as the role of high and ultra-high b-value diffusion imaging.

Diffusion Tensor Imaging (DTI): measures and interpretation

Diffusion tensor imaging (DTI) represents one of the earliest extensions of conventional DWI, incorporating directional information to model diffusion as a second-order tensor. This approach enables the characterization of anisotropic diffusion, which is particularly relevant in white matter tracts where water diffusion is directionally constrained along axonal fibers. From the diffusion tensor, several quantitative parameters can be derived, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) [14].

FA reflects the degree of directional preference of diffusion and is widely used as an indicator of white matter integrity. MD provides a measure of overall diffusivity, while AD and RD are associated with axonal integrity and myelin integrity, respectively. These metrics have been extensively applied in neurological disorders, including neurodegenerative diseases, multiple sclerosis, and traumatic brain injury, where they can detect subtle microstructural changes that are not visible on conventional imaging [14,19].

Despite its clinical utility, DTI has important limitations. The model assumes Gaussian diffusion and a single dominant fiber orientation per voxel, which is often violated in regions with complex fiber architecture, such as crossing or kissing fibers. As a result, DTI-derived parameters may lack specificity and fail to fully capture the complexity of tissue microstructure. These limitations have driven the development of more advanced diffusion models that account for non-Gaussian behavior and multi-compartmental tissue structure [17].

Diffusion Kurtosis Imaging (DKI): non-Gaussian diffusion and added value
Diffusion kurtosis imaging (DKI) extends the DTI framework by incorporating higher-order statistical moments to quantify deviations from Gaussian diffusion. Specifically, DKI measures the kurtosis of the diffusion signal, which reflects the degree of restriction and heterogeneity within the tissue microenvironment. Key parameters include mean kurtosis (MK), axial kurtosis (AK), and radial kurtosis (RK), which provide complementary information to conventional DTI metrics [3,4]. The ability of DKI to capture non-Gaussian diffusion behavior makes it particularly sensitive to microstructural complexity, such as increased cellularity, membrane density, and tissue heterogeneity. This has been demonstrated in a variety of clinical contexts, including tumor grading, neuroinflammation, and neurodegenerative diseases. For example, increased kurtosis values have been associated with higher tumor cellularity and more aggressive tumor phenotypes, while decreased kurtosis may reflect tissue degeneration or loss of structural integrity [2,20].

Recent studies have further highlighted the clinical utility of DKI in neurological disorders. In patients with encephalitis and other inflammatory conditions, DKI parameters have shown improved sensitivity compared to DTI in detecting microstructural abnormalities in both white and gray matter [2]. Similarly, DKI has been applied in the assessment of cognitive impairment and vascular disease, demonstrating its potential as a biomarker for subtle microstructural changes [20].

However, DKI requires higher b-values and more complex acquisition schemes compared to DTI, leading to longer scan times and reduced signal-to-noise ratio. These technical challenges must be carefully balanced against the potential diagnostic benefits of the technique.

Intra-voxel Incoherent Motion (IVIM): perfusion fraction and diffusion separation
Intravoxel incoherent motion (IVIM) imaging provides a unique approach to diffusion MRI by separating the contributions of molecular diffusion and microvascular perfusion within a voxel. This is achieved by modeling the diffusion signal as a bi-exponential function, with parameters representing true diffusion (D), pseudo-diffusion related to perfusion (D*), and the perfusion fraction (f) [5,6].

The ability to quantify perfusion-related effects without the use of contrast agents makes IVIM particularly attractive in clinical settings where contrast administration is contraindicated. IVIM has been applied in a variety of neurological conditions, including brain tumors, stroke, and psychiatric disorders, where it provides complementary information to conventional diffusion and perfusion imaging techniques [5,21].

In brain tumors, IVIM parameters have been shown to correlate with tumor vascularity and cellularity, aiding in tumor characterization and treatment response assessment. Similarly, in ischemic stroke, IVIM can provide insights into microvascular perfusion and tissue viability, potentially improving the assessment of the ischemic penumbra [5].

Despite these advantages, IVIM is technically challenging due to the need for multiple low and high b-value acquisitions and the inherently low signal-to-noise ratio of the perfusion-related component. Additionally, the fitting of bi-exponential models is sensitive to noise and may result in variability in parameter estimation, limiting its widespread clinical adoption [6].

Multi-compartment models: NODDI and related microstructure models
Multi-compartment diffusion models aim to provide a more biologically meaningful representation of tissue microstructure by explicitly modeling different tissue compartments within a voxel. Among these, neurite orientation dispersion and density imaging (NODDI) has gained significant attention for its ability to estimate neurite density index (NDI) and orientation dispersion index (ODI), which reflect the density and spatial organization of axons and dendrites [7].

NODDI has been widely applied in both neurological and psychiatric disorders, demonstrating sensitivity to microstructural alterations that are not detectable with DTI or DKI. For example, changes in neurite density and orientation dispersion have been reported in neurodegenerative diseases such as Alzheimer's disease, as well as in psychiatric conditions, highlighting the potential of NODDI as a biomarker of disease progression [7,22].

Recent advances in multi-shell diffusion acquisition have facilitated the implementation of NODDI and other multi-compartment models in clinical research. Comparative studies have shown that these models provide improved specificity in characterizing tissue microstructure, particularly in conditions such as multiple sclerosis, where they can differentiate between demyelination, axonal loss, and inflammation [10,16].

However, multi-compartment models require more complex acquisition protocols, including multiple b-values and diffusion directions, as well as advanced post-processing techniques. These requirements can increase scan time and computational complexity, posing challenges for routine clinical implementation.

High and ultra-high b-value diffusion: rationale and tradeoffs

High and ultra-high b-value diffusion imaging has emerged as an important approach for enhancing sensitivity to restricted diffusion and microstructural heterogeneity. By increasing the diffusion weighting, these techniques suppress the signal from freely diffusing water and emphasize contributions from more restricted compartments, thereby improving contrast in pathological tissues [9].

High b-value imaging has been shown to improve lesion conspicuity in brain tumors and enhance the detection of subtle microstructural changes in neurodegenerative diseases. Additionally, it plays a critical role in advanced diffusion models such as DKI and multi-compartment approaches, which rely on non-Gaussian signal behavior at higher b-values [9].

However, increasing the b-value comes at the cost of reduced signal-to-noise ratio and increased susceptibility to artifacts. This necessitates careful optimization of acquisition parameters and may require the use of advanced denoising and reconstruction techniques, including deep learning-based approaches, to maintain image quality [11,12].

Practical comparison of diffusion models

The selection of an appropriate diffusion model depends on the clinical question, available acquisition time, and required level of microstructural detail. While DTI remains widely used due to its simplicity and robustness, advanced models such as DKI, IVIM, and NODDI offer improved sensitivity and specificity at the cost of increased complexity.

Table. Comparison of quantitative diffusion MRI models

Model	Assumptions	Acquisition Requirements	Key Outputs	Clinical Applications
DTI	Gaussian diffusion, single tensor	≥6 directions, single-shell	FA, MD, AD, RD	White matter integrity, neurodegeneration
DKI	Non-Gaussian diffusion	Multi b-values (high b)	MK, AK, RK	Tumor grading, inflammation
IVIM	Bi-exponential (diffusion + perfusion)	Multiple low + high b-values	D, D*, f	Tumor perfusion, stroke
NODDI	Multi-compartment model	Multi-shell acquisition	NDI, ODI	Neurodegeneration, MS
High b-value DWI	Enhanced restriction sensitivity	High b-values (≥2000)	Signal contrast	Tumor detection, microstructure

Acquisition Strategies and Practical Implementation

The reliability and clinical utility of diffusion MRI depend critically on optimized acquisition strategies that balance image quality, microstructural sensitivity, and feasibility within clinically acceptable scan times. Advances in diffusion modeling have necessitated increasingly sophisticated acquisition protocols, including multi-shell sampling, higher angular resolution, and improved hardware capabilities. At the same time, practical considerations such as patient motion, signal-to-noise ratio (SNR), and standardization across sites remain key challenges in clinical implementation.

Single-shell versus multi-shell diffusion protocols

Diffusion MRI acquisitions can be broadly categorized into single-shell and multi-shell protocols, depending on the number of b-values employed. Single-shell acquisitions typically include one non-zero b-value (commonly b = 1000 s/mm²) along with a baseline (b = 0), and form the basis of conventional DTI. These protocols are widely used in clinical practice due to their relatively short acquisition times, robustness, and compatibility with standard post-processing pipelines [14].

However, single-shell acquisitions are inherently limited in their ability to characterize complex tissue microstructure. They assume Gaussian diffusion behavior and are insufficient for estimating more advanced models such as diffusion kurtosis imaging (DKI), intravoxel incoherent motion (IVIM), or multi-compartment models. In contrast, multi-shell diffusion imaging employs multiple b-values, enabling the characterization of non-Gaussian diffusion and the separation of multiple diffusion components [10].

Multi-shell protocols are essential for advanced microstructural modeling approaches such as neurite orientation dispersion and density imaging (NODDI), which require data acquired at different diffusion weightings to estimate compartment-specific parameters [7]. Additionally, multi-shell data improve the stability and accuracy of model fitting and allow for greater flexibility in post-processing, including the application of different diffusion models to the same dataset [10].

Despite these advantages, multi-shell acquisitions come with increased scan time and greater susceptibility to motion artifacts, which can limit their routine clinical use. Therefore, protocol optimization is necessary to balance the benefits of enhanced microstructural information against practical constraints in clinical settings.

Number of diffusion directions, b-value schemes, and scan time trade-offs

The number of diffusion encoding directions and the selection of b-values are critical determinants of data quality and model accuracy in diffusion MRI. For DTI, a minimum of six non-collinear diffusion directions is required to estimate the diffusion tensor, although higher numbers (e.g., 20–30 directions) are typically used to improve robustness and reduce noise sensitivity [14].

Advanced diffusion models require more extensive sampling of diffusion space. For example, DKI typically requires multiple b-values, including high b-values (≥2000 s/mm²), along with a sufficient number of diffusion directions to ensure reliable estimation of kurtosis parameters [5]. Similarly, NODDI and other multi-compartment models rely on multi-shell acquisitions with varying b-values and high angular resolution to accurately capture microstructural features [7].

The choice of b-value scheme is particularly important, as it determines sensitivity to different diffusion regimes. Low b-values are more sensitive to fast diffusion and perfusion effects, while high b-values emphasize restricted diffusion and microstructural complexity [9]. IVIM imaging, for instance, requires a combination of very low and intermediate b-values to separate perfusion-related signal from true diffusion [6,23].

However, increasing the number of b-values and diffusion directions inevitably leads to longer scan times, which can increase the likelihood of patient motion and reduce clinical feasibility. To address this trade-off, optimized acquisition schemes have been proposed that balance angular resolution, b-value distribution, and scan time. These include reduced direction schemes, optimized gradient sampling, and adaptive acquisition strategies that maximize information content while minimizing acquisition time [15].

Hardware considerations and acceleration techniques

The performance of diffusion MRI is strongly influenced by hardware capabilities, including magnetic field strength, gradient system performance, and receiver coil design. Higher field strengths, such as 3 Tesla and above, provide increased SNR, which can be leveraged to improve spatial resolution or support higher b-value acquisitions. However, higher field strengths also increase susceptibility artifacts and image distortions, particularly in echo-planar imaging sequences [1].

Gradient strength and slew rate are critical for achieving high b-values and rapid diffusion encoding. Modern MRI systems equipped with high-performance gradient systems enable stronger diffusion weighting and shorter echo times, improving both sensitivity and image quality. These capabilities are particularly important for advanced diffusion models that require high b-values and multi-shell acquisitions [9].

Recent advances in acceleration techniques have further improved the feasibility of diffusion MRI in clinical practice. Parallel imaging methods, such as sensitivity encoding (SENSE) and generalized autocalibrating partially parallel acquisitions (GRAPPA), reduce acquisition time by undersampling k-space, albeit with some loss of SNR. Simultaneous multi-slice (SMS) imaging allows multiple slices to be acquired simultaneously, significantly reducing scan time without compromising spatial resolution [15].

In addition to these conventional techniques, artificial intelligence (AI)-based methods have emerged as powerful tools for accelerating diffusion MRI acquisition and improving image quality. Deep learning approaches have been applied to denoising, reconstruction, and super-resolution, enabling faster acquisitions while maintaining or even enhancing image quality. For example, convolutional neural network-based methods have been shown to accelerate high b-value diffusion imaging and improve robustness to noise [11-13].

Quality control and standardization

Ensuring the reliability and reproducibility of diffusion MRI measurements is essential for both clinical and research applications. Quality control (QC) procedures are necessary at multiple stages, including data acquisition, preprocessing, and analysis. These procedures aim to identify and correct artifacts, assess data quality, and ensure consistency across scans and sites [15].

Phantom studies play a crucial role in QC and standardization by providing a controlled environment for evaluating scanner performance and validating diffusion measurements. Diffusion phantoms with known properties can be used to assess accuracy, precision, and stability of diffusion parameters, as well as to calibrate scanners across different sites [14].

Inter-site variability is a significant challenge in multicenter studies, where differences in scanner hardware, acquisition protocols, and preprocessing methods can introduce variability in diffusion metrics. Harmonization strategies, including standardized acquisition protocols, cross-site calibration, and advanced post-processing techniques, are essential to reduce variability and improve comparability of results [16].

Recent efforts have focused on developing standardized guidelines for diffusion MRI acquisition and analysis, as well as large-scale normative datasets to facilitate the interpretation of diffusion metrics in clinical populations. Advanced preprocessing pipelines, including denoising, motion correction, and distortion correction, further contribute to improved data quality and reproducibility [15].

The integration of AI-based tools into QC and preprocessing workflows offers additional opportunities for improving standardization. Automated quality assessment algorithms can detect artifacts and inconsistencies, while machine learning approaches can harmonize data across sites and scanners, enhancing the reliability of diffusion MRI as a quantitative biomarker [11,18].

Post-processing and Quantitative Analysis

The accuracy and clinical utility of diffusion MRI depend not only on acquisition strategies but also on robust postprocessing and quantitative analysis pipelines. Diffusion-weighted data are inherently susceptible to noise, artifacts, and geometric distortions, which can significantly bias parameter estimation if not properly corrected. Therefore, standardized preprocessing pipelines, reliable model fitting strategies, and rigorous approaches to reproducibility and harmonization are essential for ensuring the validity of diffusion-derived metrics.

Preprocessing pipelines

Preprocessing of diffusion MRI data involves a series of steps designed to improve data quality and minimize artifacts prior to model fitting. A typical preprocessing pipeline includes denoising, Gibbs ringing correction, eddy current and motion correction, and susceptibility-induced distortion correction.

Denoising is a critical first step, as diffusion MRI is particularly sensitive to noise, especially at high b-values where signal attenuation is substantial. Advanced denoising techniques based on random matrix theory, such as Marchenko–Pastur principal component analysis (MP-PCA), have been shown to effectively suppress noise while preserving structural information [24]. More recently, deep learning-based denoising approaches have been introduced, demonstrating improved performance in maintaining image quality and quantitative accuracy, particularly in high-resolution and high b-value datasets [18].

Gibbs ringing artifacts, which arise from truncation of k-space data, can introduce oscillatory patterns near sharp intensity transitions and bias diffusion metrics. Correction methods based on subvoxel shifting or local filtering are commonly applied to mitigate these effects and improve the accuracy of subsequent analyses [15].

Eddy current and motion correction are essential for addressing distortions caused by rapidly switching diffusion gradients and patient movement. Eddy currents can induce spatial shifts and scaling distortions, while subject motion introduces misalignment between diffusion volumes. Correction algorithms, such as those implemented in widely used toolboxes, simultaneously model eddy current effects and motion parameters to align diffusion-weighted images and reduce artifacts [15].

Susceptibility-induced distortions, particularly in echo-planar imaging, result from magnetic field inhomogeneities at air–tissue interfaces. These distortions can lead to geometric warping and misregistration with anatomical images. Correction methods typically involve the use of field maps or reverse phase-encoded images (e.g., topup-based approaches) to estimate and correct for susceptibility effects [15].

The combination of these preprocessing steps forms a standardized pipeline that significantly improves data quality and reliability. The order of operations is also important, with denoising and Gibbs correction typically performed prior to motion and distortion correction to maximize effectiveness.

Model fitting strategies and software

Following preprocessing, quantitative diffusion parameters are estimated using model fitting techniques that relate the diffusion signal to underlying tissue properties. The choice of fitting strategy depends on the diffusion model being used, with different approaches required for DTI, DKI, IVIM, and multi-compartment models.

For diffusion tensor imaging (DTI**)**, parameter estimation is commonly performed using linear or weighted least squares fitting, which provides efficient and robust estimation of tensor elements and derived metrics such as fractional anisotropy and mean diffusivity. However, linear fitting methods may be sensitive to noise and outliers, necessitating the use of more robust approaches such as non-linear least squares or RESTORE algorithms in certain cases [14].

In diffusion kurtosis imaging (DKI), model fitting involves estimating both diffusion and kurtosis tensors, which requires higher-order polynomial fitting and multiple b-values. Non-linear fitting methods are typically employed to improve accuracy, although they are computationally more intensive and sensitive to noise [3,4]. Careful selection of b-value ranges and regularization strategies is often necessary to ensure stable parameter estimation.

For intravoxel incoherent motion (IVIM) imaging, parameter estimation involves fitting a bi-exponential model to the diffusion signal. This process is particularly challenging due to the low signal-to-noise ratio of the perfusion-related component (D*). Both segmented fitting approaches (separating low and high b-value regimes) and full non-linear fitting methods have been proposed, each with advantages and limitations in terms of robustness and computational efficiency [6,23].

Multi-compartment models, such as neurite orientation dispersion and density imaging (NODDI), require more complex fitting procedures that incorporate multiple tissue compartments and constraints. These models typically rely on non-linear optimization techniques and may require prior assumptions or fixed parameters to ensure stability. The use of multi-shell diffusion data is essential for accurate estimation of these parameters [7].

Several software toolboxes have been developed to facilitate diffusion MRI analysis. Widely used platforms include FSL (FMRIB Software Library), MRtrix, and DIPY (Diffusion Imaging in Python), which provide comprehensive pipelines for preprocessing, model fitting, and visualization. These tools support a range of diffusion models and are widely used in both research and clinical settings. Additionally, specialized software packages are available for advanced models such as NODDI and IVIM, enabling more detailed microstructural analysis [15].

Reproducibility, test–retest reliability, and harmonization

Reproducibility is a critical requirement for the clinical translation of diffusion MRI, particularly when quantitative metrics are used as biomarkers. Variability in diffusion measurements can arise from multiple sources, including scanner hardware, acquisition protocols, preprocessing methods, and model fitting strategies. Therefore, systematic evaluation of test–retest reliability and implementation of harmonization techniques are essential.

Test–retest studies assess the stability of diffusion metrics across repeated scans under similar conditions. Metrics such as fractional anisotropy and mean diffusivity have generally demonstrated good reproducibility, particularly when standardized acquisition and preprocessing protocols are used. However, more advanced parameters, such as kurtosis or NODDI-derived metrics, may exhibit greater variability due to their increased sensitivity to noise and modeling assumptions [10,14].

Inter-site variability presents an additional challenge, particularly in multicenter studies where differences in scanner vendors, field strengths, and acquisition parameters can lead to systematic differences in diffusion measurements. Harmonization strategies aim to reduce these differences and improve comparability across sites. These approaches include standardization of acquisition protocols, cross-site calibration using phantoms, and statistical harmonization techniques applied during data analysis [16].

Phantom-based calibration is an important tool for assessing scanner performance and ensuring consistency across sites. Diffusion phantoms with known properties can be used to evaluate accuracy, precision, and temporal stability of diffusion measurements, providing a reference for quality assurance [14].

Advanced postprocessing techniques have also been developed to improve reproducibility. For example, harmonization algorithms based on machine learning can adjust diffusion metrics to account for scanner-related variability, while standardized preprocessing pipelines help reduce methodological differences between studies [15]. Recent work has also emphasized the importance of large normative datasets and reference atlases for interpreting diffusion metrics in clinical populations.

The integration of artificial intelligence into diffusion MRI analysis offers further opportunities for improving reproducibility and standardization. AI-based methods can automate preprocessing steps, detect artifacts, and enhance parameter estimation, thereby reducing operator dependence and variability. However, careful validation and standardization of these approaches are necessary to ensure their reliability and generalizability across different clinical settings [11,18].

ROLE OF ARTIFICIAL INTELLIGENCE IN DIFFUSION MRI

Artificial intelligence (AI) has emerged as a transformative force in medical imaging, with diffusion MRI representing one of the domains where its impact is particularly significant. The inherent challenges of diffusion MRI—such as low signal-to-noise ratio (SNR), long acquisition times, and complex model fitting—make it well suited for AI-driven solutions. Recent advances in machine learning and deep learning have enabled improvements in image reconstruction, acquisition efficiency, quantitative parameter estimation, and overall workflow optimization, thereby facilitating the clinical translation of advanced diffusion imaging techniques.

AI for reconstruction and denoising

One of the most prominent applications of AI in diffusion MRI is in image reconstruction and denoising. Diffusion-weighted images, particularly those acquired at high b-values, are inherently noisy due to significant signal attenuation. Traditional denoising techniques, such as those based on random matrix theory, have demonstrated effectiveness in reducing noise while preserving structural information [24]. However, deep learning-based methods have shown superior performance in maintaining image quality and quantitative accuracy.

AI-based denoising approaches typically employ convolutional neural networks (CNNs) trained on paired noisy and high-quality datasets to learn noise characteristics and suppress them effectively. These methods can improve SNR without compromising spatial resolution, enabling more reliable estimation of diffusion metrics [18]. In addition, generative models, such as generative adversarial networks (GANs), have been applied to enhance image quality by reconstructing high-fidelity images from undersampled or noisy data. These approaches can produce images with improved contrast and reduced artifacts, particularly in challenging acquisition settings [11].

Super-resolution techniques represent another important application of AI in diffusion MRI. By learning mappings between low-resolution and high-resolution images, AI models can enhance spatial resolution without increasing acquisition time. This is particularly beneficial for diffusion imaging, where high spatial resolution is often limited by SNR and scan time constraints. The combination of denoising and super-resolution enables improved visualization of fine microstructural details, which is critical for accurate diagnosis and research applications.

AI for accelerated acquisition

Long acquisition times remain a major limitation of diffusion MRI, particularly for advanced techniques requiring multi-shell sampling and high angular resolution. AI-based methods have been developed to address this challenge by enabling accelerated acquisition and reducing the need for extensive sampling.

Deep learning models can reconstruct high-quality diffusion images from undersampled k-space data, effectively reducing scan time while preserving image fidelity. For example, convolutional recurrent neural networks have been applied to accelerate high b-value diffusion imaging, allowing for faster acquisition without significant loss of information [12]. Similarly, AI approaches can predict missing diffusion directions or b-values from partially acquired datasets, enabling reduced acquisition schemes with fewer directions or shells.

These methods have significant implications for clinical practice, where shorter scan times improve patient comfort and reduce motion artifacts. Moreover, accelerated acquisition facilitates the incorporation of advanced diffusion models into routine clinical workflows, which would otherwise be limited by time constraints.

However, the success of AI-based acceleration depends on the quality and diversity of training data, as well as the ability of the model to generalize across different scanners and acquisition protocols. Careful validation is therefore essential to ensure that accelerated methods do not introduce biases or compromise quantitative accuracy.

AI for model fitting and microstructure estimation

Another key application of AI in diffusion MRI is in the estimation of quantitative parameters from diffusion data. Traditional model fitting approaches, such as least squares or non-linear optimization, can be computationally intensive and sensitive to noise, particularly for complex models such as DKI, IVIM, and NODDI.

Machine learning techniques offer an alternative approach by learning direct mappings between diffusion signals and microstructural parameters. These methods can significantly reduce computation time and improve robustness to noise and artifacts. For example, neural networks can be trained to estimate diffusion tensor parameters, kurtosis metrics, or multi-compartment model parameters directly from raw diffusion data, bypassing the need for iterative fitting procedures [25].

AI-based model fitting has also been applied to improve the stability and reproducibility of parameter estimation. By incorporating prior knowledge and regularization, these methods can reduce variability in diffusion metrics and enhance their reliability as biomarkers. Furthermore, AI approaches can integrate information from multiple imaging modalities, enabling more comprehensive characterization of tissue microstructure.

Recent developments have explored the use of AI for diffusion fingerprinting and combined diffusion-relaxometry models, which aim to simultaneously estimate multiple tissue properties from a single acquisition. These approaches have the potential to further streamline diffusion MRI workflows and expand the scope of quantitative imaging.

Pitfalls and challenges

Despite the promising advances, the application of AI in diffusion MRI is associated with several challenges that must be carefully addressed. One of the primary concerns is generalizability, as AI models trained on specific datasets may not perform well when applied to data acquired from different scanners, protocols, or patient populations. Variability in acquisition parameters and image characteristics can lead to degradation in model performance, highlighting the need for diverse and representative training datasets [11].

Explainability is another important issue, particularly in clinical settings where transparency and interpretability are essential. Many deep learning models operate as "black boxes," making it difficult to understand how predictions are generated. This lack of interpretability can limit clinical اعتماد and hinder the adoption of AI-based methods. Efforts to develop explainable AI techniques, such as attention maps and feature visualization, are ongoing but remain an area of active research.

Bias and fairness are additional concerns, as AI models may inadvertently learn biases present in training data, leading to unequal performance across different populations. This is particularly relevant in medical imaging, where demographic and clinical diversity can significantly influence imaging characteristics. Ensuring fairness and minimizing bias require careful dataset curation, validation, and monitoring.

Furthermore, the integration of AI into clinical workflows raises regulatory and ethical considerations, including data privacy, model validation, and standardization. Robust evaluation frameworks and standardized reporting guidelines are necessary to ensure the safe and effective use of AI in diffusion MRI.

Clinical Applications in Neurology

Advanced diffusion MRI techniques have significantly expanded the role of neuroimaging in the evaluation of neurological disorders. By providing quantitative measures of tissue microstructure, these techniques enable earlier detection of pathology, improved disease characterization, and more accurate monitoring of treatment response. This section reviews the clinical applications of diffusion MRI across major neurological conditions, highlighting key findings, current limitations, and future research directions.

ACUTE AND SUBACUTE ISCHEMIC STROKE

DWI in hyperacute stroke and penumbra assessment

Diffusion-weighted imaging (DWI) is a cornerstone of acute stroke imaging due to its high sensitivity in detecting cytotoxic edema within minutes of ischemic onset. Restricted diffusion, reflected as hyperintensity on DWI and reduced ADC values, corresponds to cellular swelling and failure of ionic homeostasis. This allows for early identification of infarcted tissue, even in the hyperacute phase when conventional imaging may appear normal [1].

Beyond lesion detection, DWI plays a critical role in assessing the ischemic penumbra when combined with perfusion imaging. The mismatch between diffusion-restricted regions and perfusion deficits provides an estimate of potentially salvageable tissue, guiding reperfusion therapy decisions. However, the presence of DWI-negative stroke in some patients highlights limitations in sensitivity, particularly in early or small infarcts [26].

High b-value DWI and reperfusion injury

High and ultra-high b-value diffusion imaging enhances sensitivity to restricted diffusion and has been explored for improved delineation of ischemic lesions. These techniques may provide better contrast between infarcted and viable tissue, particularly in subacute stages [9]. Additionally, advanced diffusion metrics have been investigated for detecting reperfusion injury and secondary tissue changes following recanalization therapy.

However, the use of high b-value imaging is limited by reduced signal-to-noise ratio and increased susceptibility to artifacts. Standardization of acquisition protocols and validation of clinical utility remain important areas for future research.

Limitations and future directions:

Although DWI is highly sensitive, it lacks specificity in distinguishing reversible from irreversible injury. Advanced models such as IVIM and DKI may provide additional insights into perfusion and tissue heterogeneity, but their clinical adoption requires further validation and optimization.

BRAIN TUMORS

Differentiation: tumor vs treatment effect

Diffusion MRI plays a crucial role in the characterization of brain tumors, particularly in differentiating viable tumor tissue from treatment-related changes such as radiation necrosis. Conventional ADC values are inversely correlated with tumor cellularity, with highly cellular tumors demonstrating lower ADC values. However, ADC alone may not reliably distinguish tumor recurrence from post-treatment effects due to overlapping values.

Advanced diffusion models provide improved specificity in this context. Diffusion kurtosis imaging (DKI) captures non-Gaussian diffusion behavior associated with increased tissue complexity and cellular heterogeneity. Higher kurtosis values have been associated with high-grade tumors and increased cellularity [2,20]. Similarly, intravoxel incoherent motion (IVIM) imaging enables assessment of microvascular perfusion, which can help differentiate tumor recurrence (higher perfusion fraction) from necrosis (lower perfusion) [23].

Recent studies have demonstrated that combining multiple diffusion metrics improves diagnostic accuracy. Multi-model approaches integrating DTI, DKI, and IVIM parameters have shown promise in differentiating gliomas from inflammatory lesions and in assessing tumor heterogeneity [27].

Diffusion biomarkers for grading and treatment response

Diffusion MRI-derived parameters are increasingly used as biomarkers for tumor grading and treatment monitoring. For example, DKI metrics such as mean kurtosis have been shown to correlate with tumor grade and proliferative activity, providing additional information beyond conventional imaging [20]. High b-value diffusion imaging further enhances tumor conspicuity and may improve detection of tumor margins and infiltration [9].

Diffusion metrics have also been applied in radiomics and machine learning frameworks to predict tumor genotype and treatment response, highlighting their potential role in precision oncology [28].

Limitations and future directions:

Despite promising results, variability in acquisition protocols and analysis methods limits the reproducibility of diffusion biomarkers. Standardization and multicenter validation are needed to establish their clinical utility. Future research should focus on integrating diffusion MRI with other imaging modalities and molecular data to improve tumor characterization.

Demyelinating and inflammatory disorders

NODDI and microstructure in multiple sclerosis

Diffusion MRI has become an important tool in the evaluation of demyelinating disorders such as multiple sclerosis (MS). Conventional DTI metrics, including reduced fractional anisotropy and increased diffusivity, reflect white matter damage but lack specificity in distinguishing between demyelination, axonal loss, and inflammation.

Multi-compartment models such as NODDI provide more specific microstructural information by estimating neurite density and orientation dispersion. Studies have shown that NODDI-derived metrics can detect subtle changes in both lesions and normal-appearing white matter, offering improved sensitivity to disease burden and progression [7,10].

Multishell diffusion imaging further enhances the ability to characterize MS pathology, enabling differentiation between different tissue components and improving understanding of disease mechanisms. Recent multicenter studies have demonstrated the feasibility of applying advanced diffusion models in clinical research settings [16].

Limitations and future directions:

The clinical adoption of NODDI and similar models is limited by longer acquisition times and complex post-processing requirements. Future work should focus on optimizing acquisition protocols and validating these techniques as biomarkers for disease monitoring and treatment response.

Neurodegenerative disorders

DTI, DKI, and NODDI in neurodegeneration

Diffusion MRI provides valuable insights into microstructural changes associated with neurodegenerative diseases, including Alzheimer disease, Parkinson disease, and frontotemporal dementia. DTI has been widely used to detect white matter degeneration, with reduced FA and increased MD reflecting loss of structural integrity [14].

DKI offers additional sensitivity to microstructural complexity and has been shown to detect changes in both white and gray matter in neurodegenerative conditions. For example, alterations in kurtosis metrics have been associated with cognitive impairment and disease progression, suggesting their potential as biomarkers [20].

NODDI further enhances the characterization of neurodegeneration by providing measures of neurite density and organization. Studies have demonstrated that NODDI metrics are sensitive to early changes in Alzheimer disease, even before significant atrophy is observed, highlighting their potential for early diagnosis and monitoring [8].

Limitations and future directions:
While diffusion MRI shows promise in neurodegeneration, challenges remain in standardizing protocols and interpreting findings across different populations. Longitudinal studies and integration with other biomarkers, such as PET imaging and cerebrospinal fluid analysis, are needed to establish clinical relevance.

Epilepsy and developmental disorders
Microstructure mapping and localization
Diffusion MRI plays an important role in the evaluation of epilepsy and developmental brain disorders by enabling detailed mapping of white matter microstructure. In epilepsy, diffusion abnormalities may help identify epileptogenic foci, particularly in cases where conventional MRI is negative. Alterations in diffusion metrics have been reported in both focal and generalized epilepsy, reflecting underlying microstructural abnormalities [19].

Advanced diffusion models provide additional insights into network-level changes and connectivity alterations associated with epilepsy. These techniques can improve pre-surgical planning by identifying critical white matter pathways and minimizing the risk of functional deficits.

In developmental disorders, diffusion MRI has been used to study brain maturation and detect abnormalities in white matter development. Changes in diffusion metrics may reflect alterations in myelination, axonal organization, and connectivity, providing valuable information for diagnosis and prognosis.

Limitations and future directions:
The interpretation of diffusion findings in epilepsy and developmental disorders can be challenging due to variability in normal development and disease heterogeneity. Future research should focus on establishing normative datasets and integrating diffusion MRI with functional imaging to improve localization and clinical decision-making.
Emerging and Niche Applications

Recent advances in diffusion MRI have extended its utility beyond conventional clinical applications, enabling novel approaches for tissue characterization, perfusion assessment, and multiparametric imaging. Emerging techniques such as whole-brain intravoxel incoherent motion (IVIM), ultra-high b-value diffusion imaging, and diffusion fingerprinting are expanding the scope of diffusion MRI, offering new opportunities for quantitative neuroimaging.

Whole-brain IVIM as a perfusion alternative
Intravoxel incoherent motion (IVIM) imaging has gained attention as a non-contrast technique for assessing microvascular perfusion in the brain. By modeling the diffusion signal as a combination of true molecular diffusion and pseudo-diffusion related to capillary perfusion, IVIM provides quantitative parameters such as the perfusion fraction (f), diffusion coefficient (D), and pseudo-diffusion coefficient (D*) [6,23].

Recent developments have enabled whole-brain IVIM imaging**,** making it a potential alternative to conventional perfusion techniques such as dynamic susceptibility contrast (DSC) and dynamic contrast-enhanced (DCE) MRI, particularly in patients where contrast agents are contraindicated. Whole-brain IVIM allows simultaneous assessment of diffusion and perfusion without the need for exogenous contrast, which is advantageous in populations such as patients with renal impairment or those requiring repeated imaging [23].

Studies have demonstrated that IVIM-derived perfusion parameters correlate with conventional perfusion metrics and can provide complementary information in conditions such as brain tumors and ischemic stroke. For example, IVIM has been used to evaluate tumor vascularity and distinguish between tumor recurrence and treatment-related changes [23]. Additionally, emerging applications in neurological disorders, including psychiatric conditions and sleep disorders, highlight its potential as a versatile imaging tool [21].

However, IVIM remains technically challenging due to the low signal-to-noise ratio of the perfusion component and the need for multiple low and high b-value acquisitions. Variability in parameter estimation and lack of standardized protocols limit its widespread clinical adoption. Future research should focus on improving acquisition efficiency and robustness of model fitting to facilitate routine use.

Ultra-high b-value diffusion for microstructural contrast
Ultra-high b-value diffusion imaging represents another promising development aimed at enhancing sensitivity to restricted diffusion and tissue microstructure. By increasing the diffusion weighting beyond conventional values (e.g., >2000–3000 s/mm²), these techniques suppress signal contributions from freely diffusing water and emphasize more restricted components associated with cellular structures [9].

This approach has been shown to improve lesion conspicuity and provide enhanced contrast in various neurological conditions. In brain tumors, ultra-high b-value imaging can better delineate tumor margins and identify regions of high cellularity, potentially improving tumor grading and treatment planning [9]. Similarly, in neurodegenerative diseases, increased sensitivity to microstructural alterations may allow earlier detection of pathological changes.

Ultra-high b-value diffusion is also integral to advanced diffusion models such as DKI and multi-compartment approaches, which rely on non-Gaussian diffusion behavior for accurate parameter estimation [9]. Recent studies have demonstrated its utility in identifying tumor subtypes and molecular characteristics, further supporting its role in precision imaging.

Despite these advantages, ultra-high b-value imaging is associated with significant technical challenges, including reduced signal-to-noise ratio, increased susceptibility to artifacts, and longer acquisition times. Advanced denoising and reconstruction techniques, including AI-based methods, are therefore essential to mitigate these limitations and enable practical implementation [11,12].

Diffusion fingerprinting and combined quantitative MRI approaches

Diffusion fingerprinting represents an emerging paradigm in MRI that aims to simultaneously estimate multiple tissue properties using a single acquisition. Inspired by magnetic resonance fingerprinting, this approach involves acquiring diffusion-weighted data with varying acquisition parameters and matching the resulting signal patterns to precomputed dictionaries to estimate microstructural parameters [29].

By integrating diffusion with other quantitative MRI parameters, such as T1 and T2 relaxation times, diffusion fingerprinting enables comprehensive tissue characterization within a unified framework. This approach has the potential to streamline imaging protocols, reduce scan time, and improve the accuracy and reproducibility of quantitative measurements.

Recent studies have demonstrated the feasibility of combined diffusion-relaxometry techniques, which provide complementary information about tissue composition and microstructure [30]. These approaches can enhance the characterization of complex neurological conditions by integrating multiple imaging biomarkers into a single dataset.

Moreover, advances in multi-compartment modeling and machine learning have further expanded the capabilities of combined quantitative MRI. AI-based methods can facilitate the analysis of high-dimensional data generated by these techniques, enabling more accurate and efficient parameter estimation [25].

However, diffusion fingerprinting and related approaches are still in the early stages of development and face several challenges, including the need for extensive computational resources, large training datasets, and validation across different clinical settings. Standardization of acquisition protocols and validation of clinical utility are critical for their translation into routine practice.

Standards, Validation, and Biomarker Qualification

The translation of advanced diffusion MRI techniques from research settings into routine clinical practice requires rigorous standardization, validation, and qualification as reliable imaging biomarkers. While diffusion-derived metrics offer significant potential for characterizing tissue microstructure, their clinical adoption depends on demonstrating reproducibility, robustness across sites, and clinical relevance. This section outlines key considerations for standardization, multicenter validation, and the pathway toward biomarker qualification.

Reproducibility, multicenter validation, and phantoms

Reproducibility is a fundamental requirement for any quantitative imaging biomarker. In diffusion MRI, variability can arise from multiple sources, including scanner hardware, acquisition protocols, preprocessing pipelines, and model fitting approaches. Even small differences in gradient performance, field strength, or sequence parameters can lead to significant variations in diffusion metrics, particularly for advanced models such as DKI, IVIM, and NODDI [10,14].

Test–retest studies are commonly used to assess reproducibility by evaluating the stability of diffusion metrics across repeated scans under similar conditions. Conventional parameters such as fractional anisotropy and mean diffusivity have demonstrated relatively good reproducibility, whereas more advanced metrics, including kurtosis and multi-compartment parameters, may exhibit higher variability due to their sensitivity to noise and model assumptions [14]. These findings highlight the importance of optimizing acquisition protocols and preprocessing pipelines to minimize variability.

Multicenter validation is essential for establishing the generalizability of diffusion MRI biomarkers. Large-scale studies have demonstrated that differences in scanner vendors, acquisition settings, and postprocessing methods can introduce systematic biases in diffusion measurements. For example, multishell diffusion studies in multiple sclerosis have shown that harmonized acquisition protocols and standardized analysis pipelines are necessary to achieve consistent results across sites [16]. Such efforts are critical for enabling the use of diffusion MRI in multicenter clinical trials and large cohort studies.
Phantom studies play a crucial role in standardization and validation by providing a controlled reference for evaluating diffusion measurements. Diffusion phantoms with known properties allow assessment of accuracy, precision, and temporal

stability, enabling calibration of scanners and validation of acquisition protocols [14]. Phantoms are particularly useful for cross-site comparisons, as they provide a common reference that can be used to identify and correct systematic differences between scanners.

In addition to hardware-based approaches, advanced postprocessing techniques have been developed to improve reproducibility. Harmonization methods, including statistical adjustments and machine learning-based approaches, can reduce inter-site variability and enhance comparability of diffusion metrics [15]. Furthermore, the development of large normative datasets and reference atlases has facilitated the interpretation of diffusion parameters in clinical populations, providing a framework for distinguishing pathological changes from normal variability.

Despite these advances, challenges remain in achieving full standardization of diffusion MRI. Variability in acquisition protocols and analysis methods continues to limit the comparability of studies, underscoring the need for consensus guidelines and standardized reporting practices.

Biomarker qualification and clinical translation

The qualification of diffusion MRI metrics as imaging biomarkers requires a structured process that demonstrates their reliability, clinical relevance, and utility in specific applications. Imaging biomarkers are defined as quantitative measures that reflect biological processes, disease progression, or response to therapy, and their validation involves multiple stages, including technical validation, biological validation, and clinical validation.

Technical validation focuses on the accuracy, precision, and reproducibility of the measurement. This includes evaluation of test–retest reliability, sensitivity to acquisition parameters, and robustness to noise and artifacts. Standardized acquisition protocols, quality control procedures, and validated preprocessing pipelines are essential for ensuring technical reliability [15].

Biological validation involves demonstrating that the imaging biomarker reflects underlying tissue properties or pathological processes. For diffusion MRI, this includes correlating diffusion metrics with histopathological findings, such as cellularity, myelination, and axonal integrity. Studies have shown that parameters derived from DTI, DKI, and NODDI correlate with microstructural features in various neurological conditions, supporting their biological relevance [2,20,22].

Clinical validation requires evidence that the biomarker provides clinically meaningful information that can improve diagnosis, prognosis, or treatment decision-making. For example, diffusion metrics have been used to predict tumor grade, assess treatment response, and monitor disease progression in neurodegenerative disorders. However, variability in study design and lack of standardized protocols have limited the translation of these findings into routine clinical practice [14].

For regulatory acceptance and use in clinical trials, imaging biomarkers must meet stringent criteria for reliability and clinical utility. This includes demonstrating consistent performance across different sites and populations, as well as establishing standardized thresholds or reference values. Multicenter studies and large-scale clinical trials are essential for achieving this level of validation.

Recent efforts have focused on developing frameworks for biomarker qualification, including guidelines for acquisition, analysis, and reporting of diffusion MRI studies. These initiatives aim to facilitate the integration of diffusion MRI into clinical trials and support its use as a surrogate endpoint for therapeutic interventions.

The integration of artificial intelligence into diffusion MRI analysis offers additional opportunities for biomarker development. AI-based methods can improve the robustness and reproducibility of diffusion metrics, as well as enable the extraction of complex imaging features that may serve as novel biomarkers [11,25]. However, the use of AI introduces additional challenges related to model validation, generalizability, and regulatory approval, which must be carefully addressed.

Future Directions and Research Roadmap

The rapid evolution of diffusion MRI has opened new avenues for understanding brain microstructure and its alterations in neurological diseases. Despite significant progress, several challenges remain that must be addressed to enable widespread clinical adoption and integration into precision medicine. Future research efforts should focus on harmonized acquisition strategies, integration with complementary imaging modalities, and robust clinical validation through large-scale studies and implementation frameworks.

Harmonized acquisition templates and open datasets

One of the key priorities in advancing diffusion MRI is the development of harmonized acquisition protocols that can be consistently implemented across different scanners, institutions, and patient populations. Variability in acquisition parameters, such as b-values, number of diffusion directions, and sequence design, continues to limit comparability between studies and hinders the translation of diffusion metrics into standardized biomarkers. Multicenter initiatives have demonstrated that standardized protocols, particularly for multi-shell diffusion imaging, can significantly reduce inter-site variability and improve reproducibility of advanced diffusion metrics [16].

In parallel, the creation of large-scale open datasets is essential for establishing normative reference values and enabling robust validation of diffusion biomarkers. Open-access neuroimaging repositories facilitate data sharing, promote transparency, and support the development of advanced analytical methods, including machine learning approaches. Such datasets are particularly valuable for training and validating AI models, which require diverse and representative data to achieve generalizability [25].

Furthermore, harmonization techniques, including statistical adjustments and machine learning-based approaches, are increasingly being used to align data acquired from different sites and scanners. These methods can mitigate systematic biases and improve the comparability of diffusion metrics, thereby enhancing their utility in multicenter studies and clinical trials [15]. Continued efforts to standardize acquisition protocols and develop shared datasets will be critical for advancing diffusion MRI as a reliable quantitative imaging tool.

Hybrid imaging approaches: integration with functional and metabolic imaging

Another important direction in diffusion MRI research is the integration of diffusion imaging with other imaging modalities to provide a more comprehensive characterization of brain structure and function**.** Hybrid imaging approaches that combine diffusion MRI with functional MRI (fMRI), perfusion imaging, or metabolic imaging techniques such as positron emission tomography (PET) have the potential to capture complementary aspects of brain physiology.

For example, combining diffusion MRI with fMRI enables the simultaneous assessment of structural connectivity and functional networks, providing insights into the relationship between microstructural integrity and brain function. Similarly, integration with perfusion imaging can enhance the evaluation of tissue viability in conditions such as stroke and brain tumors, where both diffusion and perfusion play critical roles [23].

Recent developments in combined quantitative MRI techniques, including diffusion-relaxometry and diffusion fingerprinting, further support the concept of multiparametric imaging. These approaches aim to simultaneously estimate multiple tissue properties, such as diffusion, relaxation times, and microstructural parameters, within a single acquisition framework [29,30]. Such integration can improve diagnostic accuracy and reduce scan time, making advanced imaging more feasible in clinical practice.

However, the implementation of hybrid imaging approaches requires careful consideration of acquisition protocols, data integration, and analysis methods. Standardization and validation of these techniques are necessary to ensure their reliability and clinical utility.

Clinical trials and implementation science priorities

The translation of diffusion MRI into clinical practice depends on robust validation through clinical trials and the development of implementation strategies that address practical and logistical challenges. While numerous studies have demonstrated the potential of advanced diffusion metrics as biomarkers, their incorporation into clinical trials remains limited.

Future research should prioritize the inclusion of diffusion MRI in prospective clinical trials to evaluate its role in diagnosis, prognosis, and treatment monitoring. Standardized protocols and harmonized analysis pipelines are essential for ensuring consistency across trial sites and enabling meaningful comparisons of results. Additionally, the development of validated endpoints based on diffusion metrics will facilitate their use as surrogate markers in therapeutic studies [14].

Implementation science approaches are also critical for bridging the gap between research and clinical practice. This includes addressing barriers such as long acquisition times, complex postprocessing requirements, and the need for specialized expertise. Advances in acquisition efficiency, automated analysis pipelines, and AI-based tools have the potential to overcome these challenges and enable wider adoption of diffusion MRI in clinical settings [11,12].

Regulatory considerations represent another important aspect of clinical translation. Imaging biomarkers must meet stringent criteria for reliability, reproducibility, and clinical relevance to gain regulatory approval. Collaborative efforts between researchers, clinicians, and regulatory agencies are needed to establish standardized guidelines and validation frameworks for diffusion MRI biomarkers.

CONCLUSION

Diffusion MRI has undergone significant evolution from a qualitative imaging tool to a powerful quantitative technique capable of probing tissue microstructure in vivo. While conventional diffusion-weighted imaging and apparent diffusion coefficient (ADC) mapping remain indispensable in clinical practice, particularly in acute neurological conditions, their limitations in capturing the complexity of biological tissues have driven the development of advanced diffusion models

[1,2]. Techniques such as diffusion tensor imaging (DTI), diffusion kurtosis imaging (DKI), intravoxel incoherent motion (IVIM), and multi-compartment models including neurite orientation dispersion and density imaging (NODDI) provide complementary insights into tissue architecture, enabling improved characterization of a wide range of neurological disorders [3,7,10,23].

These advanced methods have demonstrated substantial potential in clinical applications, including stroke, brain tumors, demyelinating diseases, neurodegeneration, and epilepsy, where they offer enhanced sensitivity to microstructural changes and may serve as quantitative biomarkers for diagnosis, prognosis, and treatment monitoring [14,20,22]. Furthermore, recent advances in acquisition strategies, high b-value imaging, and artificial intelligence have improved the feasibility and robustness of diffusion MRI, facilitating its integration into clinical workflows [9,11,12].

Despite these advancements, several challenges remain that limit the widespread adoption of advanced diffusion MRI techniques. Variability in acquisition protocols, lack of standardization, and limited reproducibility across centers continue to hinder the clinical translation of diffusion-derived metrics [15,16]. Additionally, the complexity of advanced models and the need for specialized expertise pose practical barriers to routine implementation.

Future efforts should focus on harmonizing acquisition protocols, validating diffusion metrics through multicenter studies, and establishing standardized frameworks for biomarker qualification. The integration of diffusion MRI with other imaging modalities and the incorporation of artificial intelligence-based approaches hold promise for enhancing diagnostic accuracy and enabling personalized medicine [11,25].

In conclusion, diffusion MRI represents a rapidly advancing field with significant potential to transform neuroimaging. Continued research, technological innovation, and collaborative efforts are essential to overcome existing challenges and fully realize its role as a robust and clinically meaningful imaging biomarker in neurology.

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