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WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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MINIREVIEWS

Diffusion tensor imaging pipeline measures of cerebral white matter integrity: An overview of recent advances and prospects

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Abstract

Cerebral small vessel disease (CSVD) is a leading cause of age-related micro-vascular cognitive decline, resulting in significant morbidity and decreased quality of life. Despite a progress on its key pathophysiological bases and general acceptance of key terms from neuroimaging findings as observed on the magnetic resonance imaging (MRI), key questions on CSVD remain elusive. Enhanced relationships and reliable lesion studies, such as white matter tractography using diffusion-based MRI (dMRI) are necessary in order to improve the assessment of white matter architecture and connectivity in CSVD. Diffusion tensor imaging (DTI) and tractography is an application of dMRI that provides data that can be used to non-invasively appraise the brain white matter connections *via* fiber tracking and enable visualization of individual patient-specific white matter fiber tracts to reflect the extent of CSVD-associated white matter damage. However, due to a lack of standardization on various sets of software or image pipeline processing utilized in this technique that driven mostly from research setting, interpreting the findings remain contentious, especially to inform an improved diagnosis and/or prognosis of CSVD for routine clinical use. In this minireview, we highlight the advances in DTI pipeline processing and the prospect of this DTI metrics as potential imaging biomarker for CSVD, even for subclinical CSVD in at-risk individuals.

Key Words: Diffusion tensor imaging; White matter; Cerebral small vessel disease; Pipeline processing; Tractography

Core Tip: Cerebral small vessel disease (CSVD) is a leading cause of age-related microvascular cognitive decline resulting in significant impairment. Despite the general acceptance of key terms from neuroimaging findings as observed on the magnetic resonance imaging (MRI), key questions on CSVD remain elusive. The MRI-based diffusion tensor imaging (DTI) offers non-invasive tool to quantitate brain white matter connections *via* fiber tracking that may inform the extent of CSVD-associated white matter damage. In this minireview, we highlight the advances in DTI pipeline processing and the prospect of DTI metrics as potential biomarker for CSVD amenable towards a routine clinical use.

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INTRODUCTION

Cerebral small vessel disease (CSVD), in its prevalent sporadic form, refers to a syndrome of clinical and neuroimaging findings in ageing populations that is frequently related to vascular risk factors and onset of neurological impairments including stroke, dementia, parkinsonism, gait problems, and mood disturbances[1,2]. Sporadic CSVD pathologies are often heterogeneous, as evidenced by neuroimaging findings such as lacunes, white matter hyperintensities and enlarged perivascular spaces on T2-weighted magnetic resonance imaging (MRI)[3,4]. While conventional MRI and MRI-based diffusion-weighted imaging (DWI) provide a detailed picture of the overall severity of white matter involvement, it is only capable of measuring diffusion in a single direction[5]. Therefore, improved relationships and reliable lesion studies are desired to enhance the assessment of white matter architecture and connectivity such as white matter tractography using diffusion-based MRI (dMRI)[6,7].

Within dMRI, diffusion tensor imaging (DTI) offers data that can be used to explain brain white matter connections non-invasively through fiber tracking[8]. One of the more current improvements in DTI is the advancement of models of individual patient-specific white matter tracts, namely the diffusion tensor tractography, which is thought to be suitable to examine the effect of CSVD on white matter tracts[9]. Various sets of computerized software or image pipeline processing (*i.e.*, from dMRI data capture to image processing and data interpretation) are used along the process due to a lack of standardization and variability in the reported findings[10]. As we strive to better understand this complex condition, this mini review will summarise the recent advances and prospects of DTI pipeline application for the clinical detection and assessment of the cerebral white matter integrity.

CSVD- AN OVERVIEW

CSVD is widely recognised as a neurovascular syndrome featuring clinical, cognitive, neuroimaging, and neuropathological findings that arise from damage and/disruption involving a complex neurogliovascular unit in the brain[11-13]. Due to various vascular-pathologic developments that could disrupt the perforating cerebral capillaries and arteries that supply the brain subcortical region with restricted collaterals, parenchymal damage is seen in the grey and deep white matter of the subcortical area (as shown in Figure 1)[14-16]. Consequently, CSVD imposes a significant impact on neuropsychological function as well as common neuropathological processes, and contributes significantly to development of cognitive impairment, dementia, and stroke[17-20]. Moreover, conventional vascular risk factors such as hypertension, diabetes, hyperlipidaemia and smoking have been shown to increase the risk towards development and progression of CSVD[21]. There are two main forms of CSVD which includes amyloidal CSVD [sporadic and hereditary cerebral amyloid angiopathy] and non-amyloidal CSVD (age-related and vascular risk-factor-related small vessel, *i.e.*, arteriolosclerosis)[22]. CSVD is commonly ascribed to a series of neuroimaging manifestations, consisting of recent small subcortical infarcts, lacunes, white matter hyperintensities (WMHs), cerebral microbleeds, prominent or enlarged perivascular spaces, cortical microinfarcts, and atrophy[3,23,24]. Figure 2 shows key manifestations of

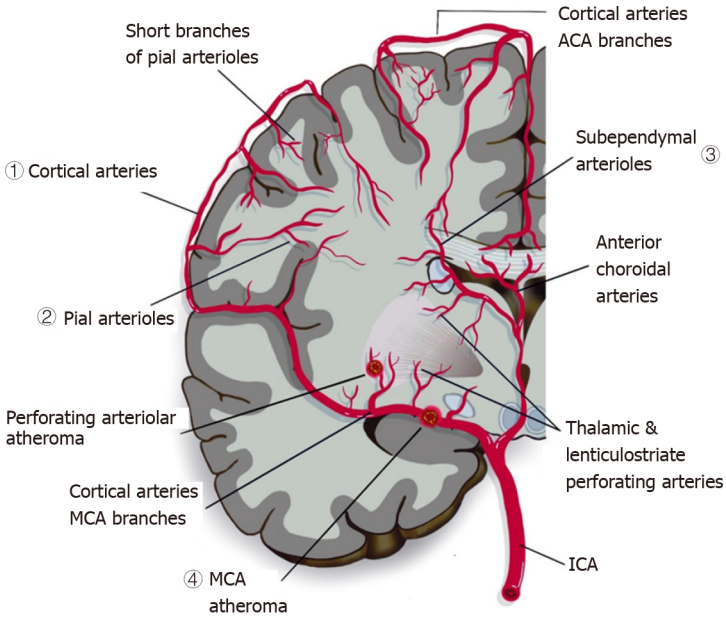

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Figure 1 Illustration of cerebral vasculature and general pathophysiology of cerebral small vessel disease. Different branches of cerebral arteries and their territories supplying the cerebral white matter: (1) cortical arteries, (2) pial arterioles that supply deep white matter, (3) short branches of anterior choroidal arteries that branch into sub-ependymal arteries, arterioles of sub-ependymal, and (4) middle cerebral artery (MCA) that branches into thalamic and lenticulostriate perforating arteries. The picture also shows branches of MCA penetrate the subcortical region of white matter and grey matter. In cerebral small vessel disease (CSVD), a thromboembolism in the MCA eventually occludes the lenticulostriate arteries, resulting in a lacunar lesion in basal ganglia. If the atheroma in the parent artery is positioned at the opening of its penetrating branches, it could lead to an acute occlusion of one or several penetrating arteries hence causing a lacunar infarct. A more extensive small vessel disease may lead to a diffused disruption of the blood-brain barrier[3]. ACA: Anterior Cerebral Artery; MCA: Middle Cerebral Artery: ICA: Internal Carotid Artery.

CSVD as streamlined for CSVD research/practical purposes by the standards for reporting and imaging of small vessel disease (STRIVE)[25]. Hence, DTI can provide a powerful insight into white matter integrity and damage found in CSVD, thus providing a possible marker for disease severity and relatable to CSVD symptoms and/or signs that would otherwise go undetected using conventional MRI [26].

DTI

DTI is a non-invasive dMRI-based method for visualizing tissue macro- and microstructures for pathological evaluation. Based on the microstructural features (*e.g.*, fiber diameter, fiber density, and myelination) that limit perpendicular diffusion and restrict water movement in specific directions, DTI assesses the free movement of water molecules inside the white-matter tracts[27]. Isotropic diffusion occurs when there are no barriers in their path, such as in a beaker of water, where molecules bumping around due to thermal action will scatter in the same way. When molecules encounter oriented barriers, however, movement is no longer dispersed evenly along all paths, and diffusion becomes anisotropic [28].

The use of DTI as a visualization tool has helped to distinguish between large, oriented macromolecule structures such as the brain white matter fiber bundles[29]. DTI tractography not only allows for the mapping of fiber tracts that are characteristic of the fundamental anatomy, but it also allows for the testing of hypotheses about age-related changes in white matter structure, as well as the distance of specific fiber tracts.

PRINCIPLE OF DTI – THEORY TO PRACTICES

The DTI parameter is reliant not entirely on static magnetic strength field, but rather on the signal-to-noise ratio (SNR) and impact of the artifact. The MRI platforms with 1.5T and 3T magnetic field strength are commonly used in routine DTI human brain scanning, although some centres have access to the 7T platform. It is acknowledged that scanning with a higher field strength improves the SNR, which equates to better results[30,31]. Aside from static magnetic fields, the number, power, and gradient coils also contribute significantly to the value of DTI data. The gradient task cycle verifies the methods for

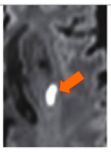
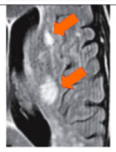
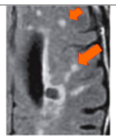
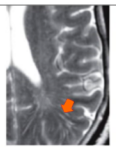
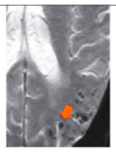
CSVD manifestation	Example Image	Description
Recent small subcortical infarcts		<20 mm in axial section, hypointense in the T1 sequence, hyperintense in T2 and FLAIR sequences and isointense in GRE-T2 sequence.
Lacunae of presumed vascular origin		Round or oval subcortical lesions 3−15 mm in diameter, filled with the CSF-like signal; the lesions cavity filled with CSF and surrounded by a hyperintense rim. Isointense in the DWI sequence, hypointense in the FLAIR and T1 sequences, and hyperintense in the T2 sequence.
White matter hyperintensities		Symmetric regardless of size; hyperintense in the T2, FLAIR and GRE-T2 (gradient-echo T2) sequences; isointense in DWI; and hypointense in T1.
Enlarged perivascular spaces (Virchow–Robin spaces)		<2 mm (mostly seen in basal ganglia); hyperintense lesions of the WM and lacunar condition but not brain atrophy; the lesions are hyperintense in T2 sequences, hypointense in FLAIR and T1 sequences, and isointense in the GRE-T2 sequence.
Cerebral microbleeds (CMBs)		Small, homogeneous lesions <10 mm in diameter, characterized by the 'blooming effect'; best seen in the gradient-echo T2 sequence (hypointense lesions); isointense in the T2, T1 and FLAIR sequences.
Brain atrophy		Brain atrophy in the context of CSVD is considered only when the patient has not suffered a stroke or head injury.

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Figure 2 Several cerebral small vessel disease manifestations according to standards for reporting and imaging of small vessel disease [63]. CSVD: Cerebral small vessel disease; CSF: Cerebrospinal fluid; WM: White matter; DWI: Diffuse-weighted imaging; FLAIR: Fluid-attenuated inversion recovery; GRE: Gradient recalled echo; CMBs: Cerebral microbleeds.

obtaining 2D images for each repetition time. The most recent scanners offer longer task cycles, allowing data to be stored in less time. Gradient force improvement allows for greater dispersion weighting and interpretation in a shorter time frame. This implies that the echo time can be reduced sequentially. Reducing the sensitivity effects will subsequently improve information conditions. Moreover, a high slew rate is desirable for DTI[6]. Nonetheless, the rapid growth and collapse of a strong gradient can cause picture-distorting eddy currents and mechanical vibrations, as well as peripheral nerve stimulation, which may result in patients' spontaneous muscle cramps. A clinical system operating for the maximum gradient amplitude is typically 40-80 milliTesla/meter (mT/m) plus 150-200 mT/m for each millisecond highest slew rate for safety reasons[32].

Non-standard apparatus offered by imaging manufacturers or built by and for investigation could improve DTI files. Using multichannel phased array coils instead of birdcage coils to improve SNR and allow equivalence scanning is a simple way to improve the quality of DTI files. However, an increase in the number of module coils may create a bias area that favors cortical exposure over deep white matter, making DTI in this region less ideal[32,33]. Without quantification, the data cannot be statistically analyzed, and visualization findings cannot be associated with scientific outcomes[34].

Visual evaluation of dMRI images can be validated by vague quantifiable measures taken from DTI files consisting of fractional anisotropy (FA), mean diffusivity (MD), and Trace (Tr). Tr of the diffusion tensor (D) indicates the total water content. Variations in Tr(D) can be recognized uniquely to variations in the formation of tissue[35]. FA calculates the relationship between the magnitude of the anisotropic element of D and the entire magnitude of D. FA values are in the limit of (0 or 1) and can be assessed in each voxel. FA is a commonly applied DTI measure that explains the intensity of diffusion anisotropy in a voxel[36,37].

DTI analyses are classified into three main groups: whole brain, regional and voxel-based methods. An increasing number of software tools are available to analyze DTI information which differ significantly in their purposes. The wide scope of analysis methods and diverse aims in software packages contributes to an absence of consistency that muddles the evaluation of DTI information and understanding the findings[38].

The whole-brain analysis technique is used to find a quantitative DTI measure from all the white matter voxels in the brain and used seed regions from all voxels in the brain[39,40]. Histogram analysis is used to summarize the DTI measured that has been obtained from the chosen voxels of interest which reveals the frequency distribution number of voxels with certain values of the diffusion amount[41,42]. Meanwhile, region-specific analysis techniques are region of interest (ROI) analysis and tractography analysis. ROI is a diffusion measure acquired from a region in a brain that is marked by manual or by automated segmentation or parcellation[43,44]. Whereas the voxel-based analysis (VBA) technique evaluates and compares DTI measurement in the tiniest imaging possible (*i.e.*, the individual voxel)[45].

Fiber tracking or tractography is a post-processing method that can effectively analyze white matter fiber bundles *in vivo*. Tractography analysis describes the statistical rebuilding of the white matter fiber bundle interpretations by integration of the local diffusion tensor information from each voxel and associated with a riddle "connecting the dots"[46,47]. Tractography is reliant on user input to identify sites in the brain through which tracts are to be rebuilt and that reliant on options are recognized to be anatomically related[48].

CLINICAL APPLICATIONS OF DTI

DTI is applied in a range of clinical situations and is not restricted to neurological purposes. DTI is employed for variable measures in medical procedures even though its efficiency remains primarily a preclinical research device. Currently, the medical use of DTI by probable clinical value is for the preparation of neurosurgical and radiotherapeutic procedures. DTI application not only offers microstructural knowledge on biological location and structure, but also macrostructural information involving the white matter tracts and connections among vital cortical and subcortical functional regions in the brain[49]. Additionally, DTI can provide complementary knowledge about the essential subcortical structure and thus can be utilized in neurosurgical and radiotherapeutic planning. Moreover, DTI is also used in the identification and follow-up of brain tumors[50,51], multiple sclerosis [52], demyelinating disorder, dementia[53-55], psychiatry[56,57] and traumatic brain injury[58].

DIFFUSION TENSOR IMAGING (DTI) PIPELINE ANALYSIS

There are tons of computerized software tools available in the literature with various functionalities, varying from data import, basic image viewing and processing, image quality improvement, registration, automatic segmentation, and DTI tractography to higher-order diffusion modelling and enhanced tractography[38,59-61]. It can be classified into different functions or applications. The general technique in DTI pipeline processing (*i.e.*, a connected series of image processing elements, in which the output becomes the input of the next image processing unit in a pipeline[62] and analysis involves a few steps, including artifacts and data acquisition techniques, quality control and pre-processing, processing and visualization, quantitative analysis, multimodal studies, and lastly the interpretation of results (Figure 3)[63].

Data acquisition is an essential step in DTI pipeline processing. Poor data acquisition can affect data quality and data analysis. Parameters that need to be considered in data acquisition include several diffusion directions, image resolution, *b*-value, *b*-value number, and average number. Table 1 shows the minimum required data acquisition parameters in DTI pipeline processing. The framework of the DTI pipeline is pre-processing, tensor estimation and fiber tracking. Due to the inadequate interoperability between the DTI analysis tools and the absence of standard DTI format[64], a lot of software bundles were developed and used to define their data format, such as Neuroimaging Informatics Technology Initiative (NIfTI)[65,66]. File formats such as dcm²nii, NIfTI tools, MRIcro and software converter package (*e.g.*, Freesurfer, SPM, Splicer) are usually utilized to transform files from the original clinical-setting such as digital imaging and communications in medicine (DICOM) format[66,67]. In tensor estimation, there are three main methods used to estimate tensors which are Linear Least Square (very simple executed in a single-step process, but it depends on hardware, size, and several datasets)[68], Weighted Linear Least Squares (quick method, but it varies on the magnitude of the MRI files *e.g.*, intensities of different DWI)[68] and Non-Linear Least Square (solved over the established system of nonlinear equations, but it also depends on the hardware and size of the dataset and may take minutes up to several hours to produce tensor estimation)[69]. Tools that can be used as tensor estimation are MedInria2[70], DTI Studio[71], Brain Voyager[72], and MRTrix[73].

Fiber tracking is the method for extraction of fiber pathways to quantify the white matter integrity [74]. The software used for fiber tracking includes DTITrack[63], Fiber navigator[70], MedInria2[70], and MRTrix[73]. The quantitative and correlation analysis consists of ROI analysis, VBA, and tract-based spatial statistics (TBSS) will be utilized to extract summary measures from either anatomical regions or the whole brain. In brief, ROI analysis is established on the manual delineation of prior certain regions of the brain or automated parcellations. VBA involved the registration of diffusion maps into a standard space to accomplish correspondences among individuals across voxel and consequently anatomical

Table 1 Minimum requirement of data acquisition in diffusion tensor imaging pipeline processing[84]

Data acquisition parameter	Minimum requirement	Comments
Field signal	1.5 T or 3T	Give a higher visual score, larger number of fibres. 7T and above – enables identification of smaller anatomical structures
Number of diffusion direction	Approximate 21	Lowest should be 6 diffusion direction, however it is advice to use more than 6 direction and can go up to 100 directions
Image resolution	depend on the FOV (usually 24 cm × 24 cm)	Large enough to prevent aliasing
B-value	0-1000 s/mm^2	500-5000+ for HARDI acquisition 2500 for q-space even higher, *e.g.*, 5-8000
Number of b-values (b = 0) images	2	About 1 per 6 diffusion images
Number of averages	NSA = 2	Can improve the SNR

T: Tesla; FOV: field of view; HARDI: High angular resolution diffusion imaging; NSA: Number of signal average; SNR: Signal to noise ratio.

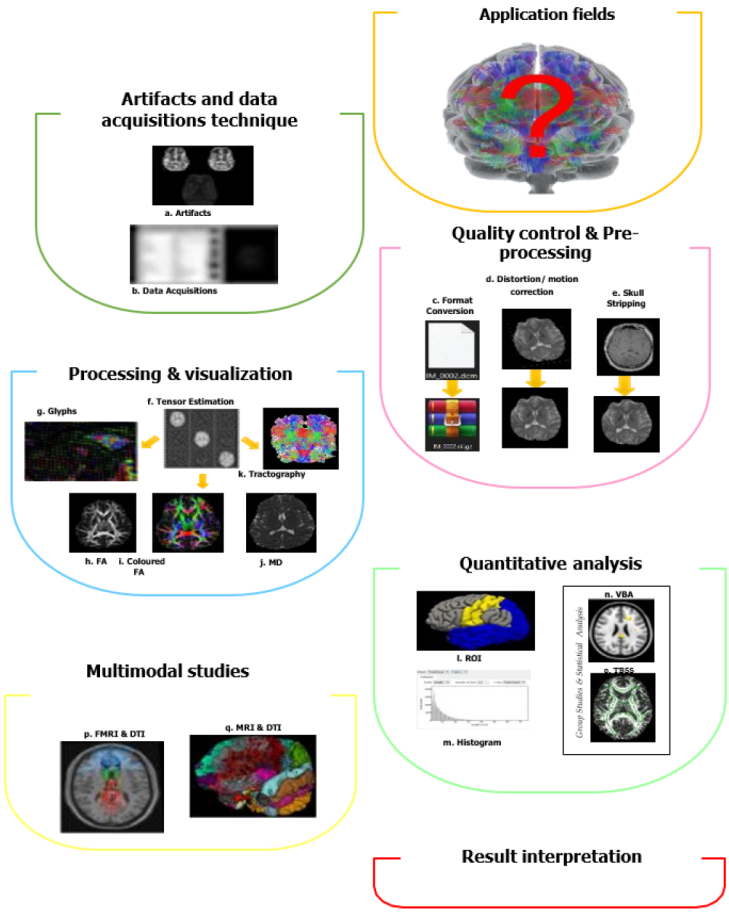

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Figure 3 Typical diffusion tensor imaging workflow[63]. The general technique in diffusion tensor imaging pipeline processing and analysis involves a few steps that include artifacts and data acquisition technique, quality control and pre-processing, processing and visualization, quantitative analysis; these can involve multimodal studies, and lastly, result interpretations. FA: Fractional Anisotropy; MD: Mean diffusivity; ROI: Region of interest; VBA: Voxel based analysis; TBSS: Tract based spatial statistics.

structures[75]. On the other hand, TBBS is a programmed technique for detecting group voxel-wise changes in the whole brain, established on the skeletonization of the group registered FA maps.

Whilst significant advancements over past two decades have been made in methodical technologies and breadth of applications, there remains no consensus on the 'gold standard' quantitative pipeline processing for CSVD studies – be it from diagnostic to prognostic implication. Most of the research teams used their own and different combinations in their pipelines[76,77] to assist with anatomical

accuracy and interpreting results in research or clinical setting are done with caution. The four pipeline processing modalities described herein (Pipeline 1 to 4) are generally adopted in assessing white matter integrity in CSVD (as summarised in Figure 4).

Pipeline 1

Pipeline 1 (P1) consists of MRI Converter version 2.1.0, Brain Software Library or FSL Toolbox functional magnetic resonance imaging, and MedINRIA 2.2[70] as shown in Figure 4. MRI Convert is a medical image file conversion utility that can convert DICOM files to other formats including NIfTI format, FSL NIfTI format, analyze format, SPM99/Analyze format, Brain Voyager, and MetaImage volume formats. It creates a directory structure based on series and subjects. These directories and output files are given default names based on the subject, study, and series information and can be changed by the user.

FMRIB's Diffusion Toolbox and BET-FSL are software tools for DWI analysis and are part of FMRIB's Software Library (FSL) that can operate on Windows and Mac. It has a user-friendly graphical interface and command-line interface. It provides tools for data processing, local diffusion modelling, and tractography which work independently from each other. NIfTI Tools installed in MATLAB-Script is a tool that is used for motion and coordination correction or cleaning process. MedINRIA is an open-source software for medical image processing and visualization[78]. It offers database management and file import, 2D to 4D image visualization, diffusion image processing, segmentation of images, filtering of images and registration of images and has a strength in visualization aids.

The first step is the DICOM data of each participant is loaded into MRI Converter, converting the DICOM file format (*.dcm*) into NIfTI file format (*.nii*). Then, the DTI files are processed using the FSL toolbox that include eddy current correction (removal of artifact) and brain extraction tool (BET) (remove the skull and non-brain structure)[79]. The required data for eddy current correction is *dti.nii*, with corrected outputs being dti.data.nii.gz and *dti.data.nii*. It is assigned with such name to make further work easier. FSL toolbox is installed using a Virtual machine workstation that serves as a platform for Linux virtualization in Windows due to the incompatibility of the FSL toolbox to be installed directly to Windows. Then, the data from the FSL toolbox will undergo cleaning using NIFTI tools installed in MATLAB. Next, the clean DTI files are then uploaded on MedINRIA[70] to further the process of tensor estimation, whole brain, and ROI tractography analysis.

Pipeline 2

Pipeline 2 (P2) consists of MRIConverter version 2.1.0 and DSIStudio[71] software (http://dsi-studio.labsolver.org/). DSI Studio is a software for diffusion MRI analysis that provides functions including reconstruction, deterministic fiber tracking, and 3D visualization[70]. Additionally, DSI Studio can rotate to the source image to correct image orientation and present a real 3D tractography representation. DSI Studio's fiber tracking algorithm is a simplified variant of the deterministic tracking algorithm that uses measurable anisotropy as the final indicator[71]. A deterministic method is used as the main axis of the tensor. The tensor aligns with the main direction of the fiber that follows the optimal path. Most likely to suggest fiber orientation for each voxel. This approach aims to find the best trade-off between valid and invalid connections[80].

The first step is to import the DICOM data of each participant into the MRI converter and converted the DICOM file format (*.dcm*) to the NIfTI file format (*.nii*). The initial stage is to mask the brain to remove non-brain structures and the skull (skull striping). Eddy corrected DTI images *with.nii*/*.bvec*/*.bval* are primarily employed in this scenario. By default, all the settings are set to their default values. The data is then opened in DSI Studio, and the output of eddy corrected DTI generated a "*.src*" file. Next, the *.src* file is reconstructed, "*.fib*" data is retrieved to track the fibers and tractography, and the FA value is then recorded.

Pipeline 3

Pipeline 3 (P3) consists of MRI Converter version 2.1.0, FSL toolbox, Diffusion toolkit, and TrackVIs[70]. DTI-Toolkit is a spatial normalization and atlas construction toolkit optimized to examine white matter morphometry using DTI data[81]. It supports a standard-based IO file such as NIfTI. Users may need to know simple Unix command lines to conduct certain tasks. It also provides a chain of tools to manipulate tensor image weight such as resampling, smoothing, warping, registration, and visualization. It is free software under public license and easily used but does not support tensor reconstruction (pre-processing support) and probabilistic fiber tractography. It applies tensor-based registration using explicit optimization of tensor reorientation analytically to give the best performance for fiber tract analysis compared to other tools[82].

TrackVIs is a complete software package that does reconstruction, fiber tracking, analysis, and visualization. It can not only handle diffusion tensor data but can also process high angular resolution diffusion imaging (HARDI) data as well as diffusion spectrum imaging data and Q-Ball imaging data. It is stand-alone, cross-platform (works on all major platforms, including Windows XP, Mac OS X, and Linux), fast and efficient. TrackVis can read in the track data file and visualizes and analyses the tracks by user's manipulation. TrackVis can read entire brain track information typically more noteworthy

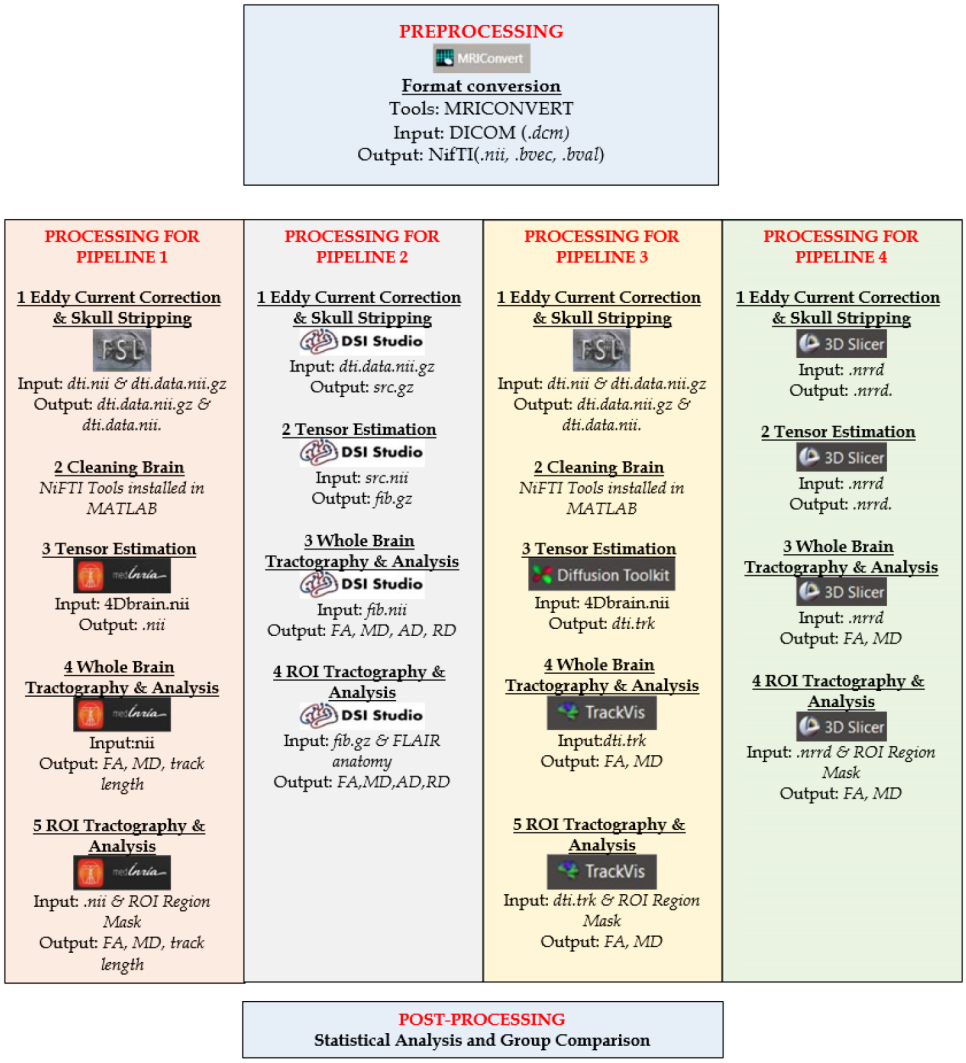

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Figure 4 Summarize processing for different pipeline processing. General methods for four pipelines processing that includes white matter hyperintensities detection and evaluation, pre-processing, processing, and post-processing. WMH: White Matter Hyperintensities; ROI: Region of interest; FA: Fractional anisotropy; MD: Mean diffusivity; AD: Axial diffusivity; RD: Radial diffusivity.

than 15 megabytes for a high-determination human output and permits the user to apply different track channels to choose and showcase fiber bundles[81].

The first step is to import DICOM data into MRI Converter and converted the DICOM file format (*.dcm*) to the NIfTI file format (*.nii*). Then, utilizing the diffusion toolkits, open the DTI file before uploading the processed data to TrackVis[71] to track the fibers and perform tractography. In the TrackVis program, track data from diffusion toolkits will be loaded either by File->Open Track or by drag-and-drop. Then, the brain image needs to be loaded for slice reference. In addition, only after the tract dataset is loaded, brain images can be loaded. TrackVis will automatically resample to match the track space from any image with different dimensions and/or voxel size. Lastly, when the tract data is loaded, acquisition of WBT and is followed by the ROI analysis value.

Pipeline 4

Pipeline 4 (P4) consists of MRI Converter version 2.1.0, and 3DSlicer[83]. 3D slicer is a software platform for the analysis and visualization including volume rendering, registration, and interactive segmentation of medical images and research in image-guided therapy[83]. It is free and open-source software that is extensible, with powerful plug-in capabilities for adding algorithms and applications. First is to load the DICOM data into the MRI Converter, converting the DICOM file format (*.dcm*) into NIfTI file format (*.nii*). Next is to upload the data through data loading, and then the data is converted into nearly raw raster data (*.nrrd*). Thus, this data can be used freely in this 3D Slicer. From this data, open the DTI file in (*.nrrd*) format, and choose the slicer DMRI program in the menu bar to undergo diffusion and to attain the tensor data. From the tensor data, we can convert the data to tract by using the draw effect tool. Then, the tract is converted into tractography by using tractography seeding in the 3D Slicer program and the tractography is then generated with the DTI parameter value. Finally, the

Table 2 Relevant previous studies applications in four pipeline processing

Pipeline processing	Relevant applications
Pipeline 1	Multiple sclerosis[52], Alzheimer's disease[53], cerebellar ataxia and cortical cerebellar atrophy[78], Krabbe disease[82], epilepsy[85], cubital tunnel syndrome[86], the white matter integrity of Alzheimer's disease[87], dementia[88]
Pipeline 2	Cubital tunnel syndrome[86], the white matter integrity of Alzheimer's disease[87], epilepsy[89], neurosurgery and brain tumour[90]
Pipeline 3	Parkinson's disease[91], Renal Failure[81,92], Epilepsy[93]
Pipeline 4	Dementia[87], neurosurgery and brain tumour[94]

same steps are repeated for ROI analysis in the 3D Slicer.

Table 2 summarises the relevant previous studies (apart from CSVD) where software in these four pipelines is utilised in image computing for quantitative imaging networks[83-94].

CLINICAL RELEVANCE OF PIPELINE PROCESSING

Taken together, DTI is a specialized diagnostic imaging tool utilizing diffusion-weighted imaging of MRI. Further studies and improvements of the DTI are warranted in advancing its utility in everyday patient care. As with any modality or imaging tool, deliberation with referring physicians, physician assistants, and nurse practitioners to increase awareness of this new option is clinically beneficial. Continuing research on its growing capabilities offer a wider adoption among health professional, especially among radiologists in interpreting the clinical merits of DTI. As radiologists see the value in DTI, more precise recommendations can be made to acquire DTI that can aid in diagnoses and/or prognoses of numerous other diseases.

CONCLUSION

This short review highlights the potential role of DTI development and technology in our pursuit to understand the pathophysiology of CSVD. We summarise key aspects of DTI pipeline analysis and the clinical significance of pipeline processing that are pertinent for CSVD, in specific. As the interests in the field undoubtedly continue to grow, DTI metrics may serve as biomarker for routine clinical use to guide diagnosis, disease progress and prognosis for CSVD natural history, from it's covert to symptomatic manifestations.

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FOOTNOTES

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