



Novel image processing techniques to better understand white matter disruption in multiple sclerosis[☆]

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Abstract

In Multiple Sclerosis (MS) patients, conventional magnetic resonance imaging (MRI) shows a pattern of white matter (WM) disruption but may also overlook some WM damage. Diffusion tensor MRI (DT-MRI) can provide important in-vivo information about fiber direction that is not provided by conventional MRI. The geometry of diffusion tensors can quantitatively characterize the local structure in tissues. The integration of both conventional MRI and DT-MRI measures together with connectivity-based regional assessment provide a better understanding of the nature and the location of WM abnormalities. Image processing and visualization techniques have been developed and applied to study conventional MRI and DT-MRI of MS patients. These include methods of: Image Segmentation for identifying the different areas of the brain as well as to discriminate normal from abnormal WM, Computerized Atlases, which include structural information obtained from a set of subjects, and Tractographies which can aid in the delineation of WM fiber tracts by tracking connected diffusion tensors. These new techniques hold out the promise of improving our understanding of WM architecture and its disruption in diseases such as MS. In the present study, we review the work that has been done in the development of these techniques and illustrate their applications.

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1. Introduction

Multiple Sclerosis (MS) is considered an autoimmune disease, in which patients exhibit inflammatory processes of demyelination in the central nervous system. WM, cortical gray matter (GM) and basal ganglia regions have all been reported to be adversely affected by the disease processes of MS. In conventional magnetic resonance imaging (MRI), MS lesions produce a hyper-intense signal in both proton density (PD) and T2-weighted images, while the hypo-intense T1-weighted lesions are considered to be chronic lesions. In MS patients, WM is likely to be disrupted in areas not apparent on conventional T2-weighted MRI. Abnormalities of normal appearing white matter (NAWM) on T2-weighted MRI have been detected using magnetization transfer (MT) imaging [1,2], diffusion tensor MRI (DT-MRI) [3–7] and MR spectroscopy [8,9].

DT-MRI proposed initially by Basser et al. [10] can provide important in-vivo information about fiber direction that is not provided by conventional MRI. The geometry of diffusion tensors can quantitatively characterize the local structure in tissues. In the brain's WM, the mobility of the water is restricted by the axons that are oriented along the fiber tracts, and the direction of highest diffusivity coincides with the tissue's fiber tract axis [10,11]. Measurements derived from DT-MRI acquisitions can include fractional anisotropy (FA), a measure of the anisotropy of diffusion direction, and the apparent diffusion coefficient (ADC), a measure of the amount of water diffusion in tissue [4,7,12–14].

Often MS patients present with increased ADC in the region of the lesions [7,12] as well as in the NAWM [12], and also exhibit a decrease in FA. Ciccarelli et al. [4] studied the NAWM in MS patients and found that the FA decreases in supratentorial and infratentorial NAWM, but increased in basal ganglia, which may result from axonal degeneration due to fiber transection in remote focal lesions. An extended review of the properties and applications of DT-MRI, and their use in the study of MS can be found in Goldberg-Zimring et al. [15].

In the present study, we review the work, which has been done in the development of three image processing and visualization techniques: segmentation, atlasing and tractography, and illustrate their application. These new techniques hold out the promise of improving our understanding of WM architecture and its disruption in diseases such as MS.

2. Segmentation

Image segmentation strategies have been developed with the aim of identifying WM, GM, and cerebro-spinal

fluid (CSF), as well as discriminating between normal and abnormal WM. The automated identification of WM signal abnormalities from dual-echo brain images of MS patients has been the subject of intensive research over the past years. Several groups have used some combination of multivariate cluster analysis in the signal intensity domain and morphometric tools (such as connectivity and opening/closing operations). Others have attempted to leverage stereotactic principles to obtain approximate boundaries of “tissue” interfaces [16]. The approach of template driven segmentation [17], combines a statistical signal-intensity based classification algorithm with anatomical context provided by a digital atlas of the brain. This approach provides segmentations of WM abnormalities with very high reproducibility and accuracy as compared to other segmentation methods [18].

3. Atlasing

Computerized atlases that represent information in a more practical and quantitative manner than conventional textbook atlases are becoming available. They often include information obtained from a set of subjects, as opposed to a single individual as used in most paper atlases, making them more representative of a population. These methods also enable the calculation of normal shape variations, such as in [19,20]. Recent work has been carried out in the construction of inter-subject atlases from DT-MRI data. This work has investigated registration schemes that leverage the capacity of DT-MRI data to provide both orientation and anisotropy information regarding WM fiber tracts. Jones et al. [21] described spatial averaging of scans from ten healthy adults, and demonstrated success in bringing fiber tracts into correspondence. In addition the recent publication [22] successfully extracted certain corresponding fiber tracts in a group of ten subjects, and then detected a different pattern of anisotropy along a certain tract in an adrenoleukodystrophy patient as compared to the healthy subjects. The feasibility of interactive selection of specific tracts has also been recently demonstrated [23]. In a study of pyramidal tracts in MS subjects [12] the feasibility of extracting tracts from scans of the patients was demonstrated. Similar in [20], Park et al. [24] created an atlas by averaging DT-MRI images.

DT-MRIs were aligned using a non-linear registration utilizing all the tensor components. The topology and morphology representative of a group of subjects is rendered by the combination of the intensity average and the shape average derived from the mean of deformation fields.

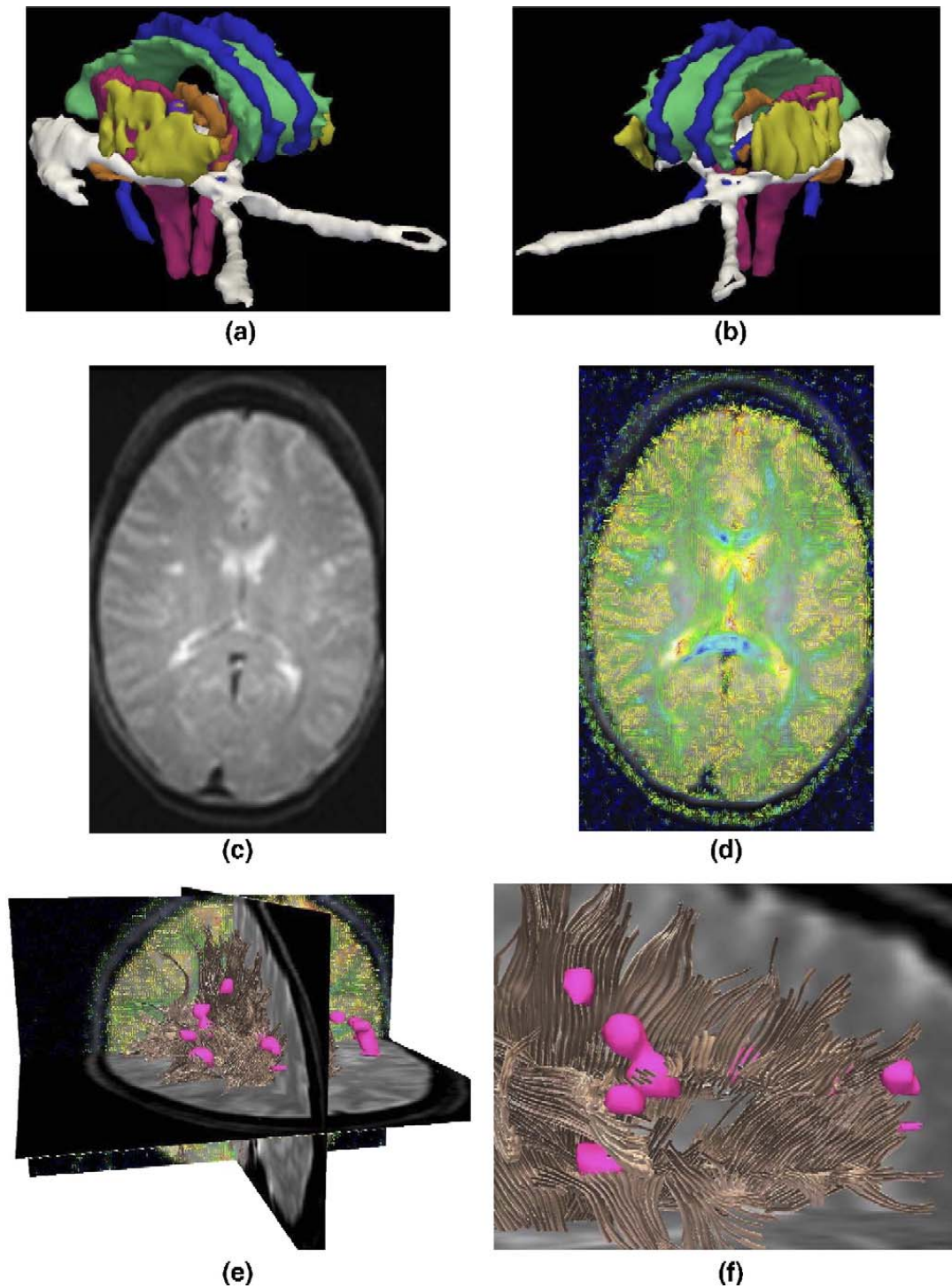


Fig. 1. A WM tract atlas presented from 2 different views (a) and (b) showing the following tracts, Cingulum (dark blue), Corpus Callosum (green), Fornix (brown), Capsula Interna (magenta), Tractus Corticospinalis (dark pink), Capsula Externa (yellow) and Optical Tract (white). (c) The baseline source of a DT-MRI scan presenting MS lesions. (d) The reconstructed DT image, color-coded with red where the diffusion is most isotropic and blue where the diffusion is most anisotropic. Note the increased isotropic diffusion in the WM lesions while the NAWM present a more generalized anisotropic diffusion. (e) WM fibers together with MS lesions are presented in the brain's right hemisphere showing the contribution of the tractography to study MS lesions, as compared to lesions' studies where only conventional MRI is used (brain's left hemisphere). (f) A zoomed view of the MS lesions and the WM fibers. Note how fibers clearly pass through some lesions.

4. Tractography

In DT-MRI, a tensor describes the local water diffusion per voxel. Such a tensor may be represented by a 3×3 symmetric matrix obtained from measurements of diffusion acquired in several directions. Tensors are often modeled as ellipsoids in which the primary diffusion directions (eigenvectors) and their respective magnitudes (eigenvalues) are represented by the ellipsoids' semi-axes. Isotropic diffusion in which the magnitude of the diffusion is equal in all directions (as in the adult brain's GM and CSF) is represented by a sphere, while anisotropic diffusion (as in the brain's WM) is represented by ellipsoids with variable magnitude of their semi-axes. Westin et al. [25] decomposed the diffusion tensor into linear (diffusion mainly in the direction of the largest eigenvalue), planar (diffusion restricted to a plane spanned by the two eigenvectors of the two largest eigenvalues) and spherical. The density of the fibers, the degree of myelination, the average fiber tract diameter and the directional similarity of the fibers in the voxel are factors affecting the shape of the diffusion ellipsoid [25]. The eigenvector having the largest eigenvalue represents the fiber's direction; therefore it is possible to assess a bulk average of the *in vivo* axonal connectivity using DT-MRI.

The first step in the construction of fiber tracts is tensor visualization by representing the information contained in DT-MRI data [26–28]. In [27–29] headless arrows were used to represent the in-plane component of the measured fiber direction, with the length of the arrows being proportional to the relative anisotropy. These approaches allow the construction of three dimensional (3D) tractographies, which can aid in the delineation of WM fiber tracts, by tracking connected diffusion tensors using the tensors as projection operators [25,30–32]. Mori et al. [22] initiated the tracking from a seed pixel and propagated a line in both the retrograde and orthograde directions according to the largest eigenvector at each pixel. They established two different thresholds in order to define where to terminate the tracking of each fiber. The tracking was performed for every pixel inside the brain, but they only kept those fibers, which penetrated previously defined regions of interest. Applying this same technique, Wakana et al. [33] reconstructed the 3D trajectories of 17 prominent WM tracts.

Graphical examples of the above image processing and visualization techniques for the study of MS are presented in Fig. 1.

5. Conclusions

The integration of both conventional MRI and DT-MRI measures together with connectivity-based regional assessment provide a better understanding of the nature

and the location of WM abnormalities. The relationship between WM disruption, WM connectivity and clinical measures will potentially allow clinicians to better correlate between fiber tract disruption and MS symptoms such as cognitive impairment. Furthermore, it would ultimately lead to improved monitoring of patients, better prediction of the courses of the disease, and more rapid assessment of new treatments or therapies.

Take-home messages

- MS is considered an autoimmune disease, in which patients exhibit inflammatory processes of demyelination the central nervous system.
- Image segmentation strategies have been developed with the aim of identifying white matter, gray matter, and cerebro-spinal fluid, as well as discriminating between normal and abnormal white matter.
- Computerized atlases represent information in a more practical and quantitative manner than traditional atlases. They often include information obtained from a set of subjects, making them more representative of a population.
- DT-MRI can provide in-vivo information about fiber direction that is not provided by conventional MRI. The geometry of diffusion tensors can quantitatively characterize the local structure in tissues.
- Diffusion tensor magnetic resonance imaging provides both orientation and anisotropy information regarding white matter fiber tracts.
- Tensor visualization allows the construction of three dimensional tractographies, which can aid in the delineation of white matter fiber tracts.

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Oral CD3-specific antibody suppresses autoimmune encephalomyelitis by inducing CD4+CD25-LAP+ T cells.

A major goal of immunotherapy for autoimmune diseases and transplantation is induction of regulatory T cells that mediate immunologic tolerance. The mucosal immune system is unique, as tolerance is preferentially induced after exposure to antigen, and induction of regulatory T cells is a mechanism of oral tolerance. Parenteral administration of CD3-specific monoclonal antibody is an approved therapy for transplantation in humans and is effective in autoimmune diabetes. In this study, Hirofumi O. et al. (*Nat Medicine* 2006; 12: 627-35) found that orally administered CD3-specific antibody is biologically active in the gut and suppresses autoimmune encephalomyelitis both before induction of disease and at the height of disease. Orally administered CD3-specific antibody induces CD4+CD25-LAP+ regulatory T cells that contain latency-associated peptide (LAP) on their surface and that function in vitro and in vivo through a TGF-beta-human autoimmune conditions.