# Role of MRI diffusion tensor imaging in assessment of normal appearing white matter in cases of multiple sclerosis

Thesis
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# Abstract

The study showed that the normal appearing white matter is pathologically involved in the majority of our patients (84%) and the degree and distribution of involvement has direct relation to some morphologic features (brain atrophy and T2 burden of the disease) that reflect the disease severity and duration. The study showed that the NAWM changes are not directly related to the largest plaques or to the regions of black holes formation on T1 WIs. The aim of our study was to evaluate the role of DTI in the assessment of normal appearing white matter in patients with multiple sclerosis. Changes in the NAWM were examined and their relation to other morphologic MR features was evaluated.



**Key words:**

**EPI- AC-3D- DIS-** NAWM

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# List of Abbreviations

| | |
|---|---|
| **MS** | Multiple sclerosis |
| **3D** | 3-Dimensional |
| **ADC** | Apparent Diffusion Coefficient |
| **(RR) MS** | Relapsing- Remittent MS |
| **CC** | Corpus Callosum |
| **(PP) MS** | Primary- Progressive MS |
| **CNS** | Central Nervous System |
| **DMDs** | Disease modifying drugs |
| **AC** | Anterior commissure |
| **MD** | Mean diffusivity |
| **US** | United states |
| **Cst** | Corticospinal Tract |
| **(SP) MS** | Secondary- progressive MS |
| **DT** | Diffusion Tensor |
| **DTI** | Diffusion Tensor Imaging |
| **IP** | International panel |
| **DTT** | Diffusion Tensor Tractography |
| **DW** | Diffusion Weighted |
| **NABT** | Normal appearing brain tissue |
| **EPI** | Echo Planar Imaging |
| **FA** | Fractional Anisotropy |
| **DIT** | Dissemination in time |
| **CIS** | Clinically isolated syndrome |
| **BOD** | Burden of disease |
| **MR** | Magnetic Resonance |
| **MRI** | Magnetic Resonance Imaging |
| **MRS** | MR spectroscopy imaging |
| **ODF** | Orientation distribution function |

| | |
|---|---|
| **PMAs** | Primary Motor Areas |
| **DIS** | Dissemination in space |
| **ROI** | Regions of Interest |
| **CMSC** | Consortium of MS centers |
| **SNR** | Signal-To-Noise Ratio |
| **DICOM** | Digital imaging and communication in medicine |
| **MT** | Magnetizing transfer |
| **T2WI** | T2 Weighted Image |
| **unc** | Uncinate Fasciculus |
| **WHO** | World Health Organization |
| **WM** | White Matter |
| **SE** | Spin echo |
| **NAWM** | Normal appearing white matter |

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# Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating condition of the central nervous system (CNS) that is generally considered to be autoimmune in nature. White matter tracts are affected, including those of the cerebral hemispheres, infratentorium, and spinal cord. MS lesions, known as plaques, may be detected anywhere in the white matter with resulting diverse clinical presentations. Continuing lesion formation in MS often leads to physical disability and, sometimes, cognitive decline. (Olivier et al., 2008)

Several methods have been proposed, mainly using conventional MR modalities like T1, FLAIR or T2 images and enhanced MRI to delineate lesions. Conventional MR techniques cannot give detailed information about the integrity and location of WM tracts. Enhanced MRI is reported as the most sensitive measure of short-term MS activity and is widely used to monitor disease evolution, either natural or modified by treatment. (Ender et al., 2007)

Trials have shown that an early diagnosis can make a big difference to the efficacy of MS drug treatments. Non conventional MR techniques are becoming increasingly important in preclinical and clinical trials as companies move forward in developing disease modifying drugs (DMDs). (Olivier et al., 2008)

Diffusion MRI is one of the non-conventional MRI techniques used for assessment of multiple sclerosis. The potential of diffusion MRI is based on the fact that, while diffusing, water molecules probe tissue structures at a microscopic scale. During typical diffusion periods, water molecules move in the brain on average over distances bouncing, crossing or interacting with many tissue components such as cell

membranes, fibers or macromolecules. The overall effect observed in a diffusion MRI reflects on statistical basis as the displacement distribution of water molecules present within a voxel. (Mori & Van Zijl, 2002)

In WM fiber tracts, organized bundles of axonal membranes and myelin sheaths present substantial barriers to diffusion, especially in directions perpendicular to that of the fibers. The architecture of the axons in parallel bundles, and their myelin sheaths, facilitate the diffusion of the water molecules preferentially along their main direction. Such preferentially oriented diffusion is called anisotropic diffusion (directionally dependent). (Mori & Van Zijl, 2002)

The emergence of diffusion tensor imaging (DTI) is of great interest in MS. DTI probe the details of water diffusion within tissues, and could therefore reveal alterations in normal appearing white matter fibers before being visible in conventional MRI. Diffusion tensor magnetic resonance imaging can provide qualitative and quantitative information about white matter location, orientation and the directionality (anisotropy) of water diffusion along a vector in 3-dimensional space. (Olivier et al., 2008)

The 3D imaging of anisotropy is an extension of diffusion MRI. If a series of diffusion gradients are applied that can determine at least 3 directional vectors, it is possible to calculate, for each voxel, a tensor that describes the 3-dimensional shape of diffusion. The fiber direction is indicated by the tensor's main eigenvector. This vector can be color-coded, yielding a cartography of the tracts' position and direction. The brightness is weighted by the fractional anisotropy which is a scalar measure of the degree of anisotropy in a given voxel (Lazar et al., 2003).

Imaging findings include the apparent diffusion coefficient (ADC), which is a measure of the magnitude of molecular motion divided by

overall diffusivity; fractional anisotropy (FA), which is the measure of the portion of the diffusion tensor that results from anisotropy (ie, a measure of the directionality of the molecular motion of water); Mean diffusivity (MD) or trace is a scalar measure of the total diffusion within a voxel. These measures are commonly used clinically to localize white matter lesions that do not show up on other forms of clinical MRI. (Lazar et al., 2003)

Various studies have demonstrated potential advantages of DTI in the diagnosis and follow-up of MS lesions. The technique is reported to be more sensitive with regard to white-matter abnormalities. It can be used to evaluate lesions with destructive pathology or acuity and can provide data regarding abnormalities of the normal-appearing white matter. It can also evaluate white matter adjacent to the MS lesions thus showing the actual extent of the disease. (Wu et al., 2008)

# Aim of work and methods

To evaluate the role of DTI in the examination of the brain white matter that shows normal appearance on conventional MRI sequences in patients with MS. Thus assessing its ability to detect early abnormalities at diffusion level.

## Multiple sclerosis

Multiple sclerosis (MS) is a disease in which the nerves of the central nervous system (brain and spinal cord) degenerate. Myelin, which provides a covering or insulation for nerves, improves the conduction of impulses along the nerves and also is important for maintaining the health of the nerves. In multiple sclerosis, inflammation causes the myelin to disappear. Consequently, the electrical impulses that travel along the nerves decelerate, that is, become slower. In addition, the nerves themselves are damaged. As more and more nerves are affected, a person experiences a progressive interference with functions that are controlled by the nervous system such as vision, speech, walking, writing, and memory. (Olivier et al., 2008)

About 350,000 people in the U.S. have multiple sclerosis. Usually, a person is diagnosed with multiple sclerosis between 20 and 50 years of age, but multiple sclerosis has been diagnosed in children and in the elderly. Multiple sclerosis is twice as likely to occur in Caucasians as in any other group. Women are twice as likely as men to be affected by multiple sclerosis earlier in life. In Egypt a related study was conducted in 2008. It shows that MS cases are 1.4 percent of all neurological diseases. The approximate total figure of patients in Egypt is around 50,000. (ESNPN, 2013)

## Causes of multiple sclerosis

The cause of multiple sclerosis is still unknown. In the last 20 years, researchers have focused on disorders of the immune system and genetics for explanations. The immune system is the body's defender and is highly

organized and regulated. If triggered by an aggressor or foreign object, the immune system mounts a defensive action which identifies and attacks the invader and then withdraws. This process depends upon rapid communication among the immune cells and the production of cells that can destroy the intruder. In multiple sclerosis, researchers suspect that a foreign agent such as a virus alters the immune system so that the immune system perceives myelin as an intruder and attacks it. The attack by the immune system on the tissues that it is supposed to protect is called autoimmunity, and multiple sclerosis is believed to be a disease of autoimmunity. While some of the myelin may be repaired after the assault, some of the nerves are stripped of their myelin covering (become demyelinated). Scarring also occurs, and material is deposited into the scars and forms plaques. (Ender et al., 2007)

### Multiple sclerosis genetics

Although its role is unclear, genetics may play a role in multiple sclerosis. European gypsies, Eskimos and African Bantu essentially do not develop multiple sclerosis, while Native Indians of North and South America, Japanese and other Asian groups have a low incidence. The general population has less than a one-percent chance of developing multiple sclerosis. The chance increases in families where a first-degree relative has the disease. Thus, a brother, sister, parent, or child of a person with multiple sclerosis stands a one-percent to three percent chance of developing multiple sclerosis. Similarly, an identical twin runs a nearly 30% chance of acquiring multiple sclerosis whereas a non-identical twin has only a 4% chance if the other twin has the disease. These statistics suggest that genetic factors play a major role in multiple sclerosis.

However, other data suggest that environmental factors also play an important role. (BOT et al., 2009)

### Histopathology of MS

It is not clear how the plaque evolves over time. MRI investigations have shown that blood-brain barrier is disrupted at the onset of symptoms, but it is not known yet whether demyelination precedes or is secondary to inflammation. The current view on this matter is that acute inflammatory response of lymphocytes, plasma cells and macrophages can produce demyelination by direct or indirect mechanisms. The macrophages in those lesions contain myelin fragments or myelin breakdown products. Lymphocytes contribute to pathologic processes by means of antibody- and cell-mediated immunity (direct mechanism) or by secretion of lymphokines and cytokines (indirect mechanism.)

The following ultrastructural characteristics are frequently found in the plaque:

- Separation of the outer lamellae of the myelin sheath, degenerative changes in myelin, infiltration with macrophages or microglia with phagocytosis of myelin and preservation of axons.

According to histologic criteria, the CNS lesions in MS are classified as early active, inactive, early remyelinating, and late remyelinating.
(Bjartmar & Trapp, 2001)

- **Assessment of Severity and Possibility for Remyelination**

The severity of demyelination may be assessed by relative preservation or destruction of oligodendrogliocytes. It is demonstrated that early in the

course of the disease, more oligodendrogliocytes are preserved in the plaque; thus some degree of remyelination remains possible. In other patients, there is a complete loss of oligodendrogliocytes. In this group of patients, possibility of remyelination is dramatically decreased. These observations may also imply that heterogeneous mechanisms are responsible for the disease induction in different patients. (Bjartmar & Trapp, 2001)

### Types of multiple sclerosis

There are different clinical manifestations of multiple sclerosis. During an attack, a person experiences a sudden deterioration in normal physical abilities that may range from mild to severe. This attack, sometimes referred to as an exacerbation of multiple sclerosis, typically lasts more than 24 hours and generally more than a few weeks (rarely more than four weeks).

About 65%-80% of individuals begin with relapsing-remitting (RR) MS, the most common type. In this type, they experience a series of attacks followed by complete or partial disappearance of the symptoms (remission) until another attack occurs (relapse). It may be weeks to decades between relapses. (Naismith et al., 2009)

In primary-progressive (PP) MS, there is a continuous, gradual decline in a person's physical abilities from the outset rather than relapses. About 10%-20% of individuals begin with PP-MS.

Those beginning with RR-MS can then enter a phase where relapses are rare but more disability accumulates, and are said to have secondary-progressive (SP) MS. About 50% of RR-MS individuals will develop SP-