Magnetic Resonance Imaging and Spectroscopy: Insights into the Pathology and Pathophysiology of Multiple Sclerosis.

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1. INTRODUCTION

Since the time that Ormerod, du Boulay, and McDonald wrote their chapter on the neuroimaging of multiple sclerosis (MS) for the first edition of this volume, continuing advances in the field of magnetic resonance (MR) and MR imaging (MRI) have made tremendous impacts in our understanding of this disease. Over the last few years, findings from (i) “conventional” MRI techniques [e.g., T₂-weighted imaging, proton-density-weighted imaging, and T₁-weighted imaging] – as well as those from (ii) more-recently developed “non-conventional” MRI techniques [e.g., magnetization-transfer imaging (MTI), diffusion-weighted imaging (DWI), diffusion-tensor imaging (DTI), proton magnetic resonance spectroscopy (¹H-MRS), and functional MRI (fMRI)] and (iii) MRI-based estimates of brain and spinal cord atrophy – have converged with findings from other areas of MS research (e.g., histopathological and clinical research) in order to give us a more comprehensive picture of MS pathology and pathophysiology. Given that a number of excellent reviews have been written on this topic in recent years³-⁴, the purpose of the present chapter is to describe some of the MRI techniques that are most-commonly used in the study of MS and to summarize some of the main aspects of our MRI-based understanding of MS. First, however, we will briefly review some of the relevant aspects of our current understanding of the pathology and pathophysiology of MS.

1.1. THE PATHOLOGY AND PATHOPHYSIOLOGY OF MULTIPLE SCLEROSIS

The pathological hallmark of MS is the presence of demyelinating lesions (also referred to as MS plaques) within the central nervous system (CNS) that are disseminated in both space and time⁵. Acute and sub-acute plaques are associated with acute inflammation and myelin breakdown. Chronic plaques are well-demarcated areas within the white matter that are hypoxic and characterized by myelin loss and astrocytic scar formation⁶. Although usually described as being “relatively spared,” axons are injured and their density is decreased in both types of demyelinating lesions.

The overt, symptomatic “attacks” of MS that signal the usual initial “relapsing-remitting” (RR) stage of the disease are generally attributed to focal inflammation, which is associated with axonal injury and demyelination that result in slowing and/or blockade of axonal conduction. Conversely, the remission of symptoms during this stage is generally attributed to a combination of (i) the resolution of inflammation, (ii) the insertion of new sodium channels across demyelinated segments of axons, and (iii) the remyelination of axons. The majority of patients will eventually enter a “secondary-progressive” (SP) stage of the disease in which there is progressive neurological disability that is speculated to result from (i) the eventual failure of remyelination, (ii) gliosis, and (iii) irreversible axonal injury and degeneration. Indeed, as reviewed by Rieckmann and Smith² and by Bjartmar and Trapp¹³, MS is no longer viewed as simply being a disease of inflammation and demyelination of the white matter: rather, axonal degeneration and neuronal damage throughout the brain are now accepted as being prominent features of MS – even early on in the disease.

1.2. SOME RECENT MRI-BASED INSIGHTS INTO MULTIPLE SCLEROSIS

As we will soon see, insights into the pathology and pathophysiology of MS have been greatly advanced by information obtained using MRI. For example, it is now evident that the so-called “normal-appearing” white matter (NAWM, i.e., white matter that appears normal on gross pathological examination or on conventional MRI) in patients with MS is, in fact, far from normal; this is true both on appropriate histological analysis¹⁴,¹⁵, as well as on non-conventional MRI measures including MTI¹⁶, DWI¹⁷, DTI¹⁸, and ¹H-MRS¹⁹-²⁰. Indeed, further changes in patients’ NAWM may become visible on these measures months – if not years – before the lesions associated with their MS become detectable on conventional MRI: this is true for MTI²¹, DWI²², and ¹H-MRS²³-²⁴.

In addition to this pathology of NAWM, there is now growing evidence for a significant involvement of the normal-appearing grey matter (NAGM) of the cerebral cortex in MS. Again, this is true both on histological analysis²⁵,²⁶, as well as on non-conventional MRI measures including MTI²⁷,²⁸, DWI²⁹, and ¹H-MRS³⁰,³¹. Furthermore, there is now evidence from fMRI for adaptive cortical reorganization in patients with MS in the absence of neurological impairment: a finding which suggests that the extent of cortico-functional pathology is greater than that which is manifest clinically²⁰,³²-³⁴. Finally, there is also now MRI-based evidence that brain and spinal cord atrophy (which reflect destructive, irreversible pathology) are common – even early on in the course of the disease³⁵.
Of course, all of these aforementioned MR measures that have contributed to our increased understanding of MS are only surrogate markers for different aspects of the pathological changes that accompany the disease. In order to better appreciate what changes in these MR surrogates mean, we will now review some of the MR techniques that are currently being used to study MS – first the conventional ones and then the non-conventional ones. We will then go on to review some of the findings regarding MRI-based analyses of cerebral atrophy in patients with MS.

2. CONVENTIONAL MAGNETIC RESONANCE IMAGING TECHNIQUES

The conventional MRI techniques used to study MS patients produce images that reflect the physico-chemical state of protons that are present mainly in the water in the tissue that is being imaged. Contrast in such images is derived primarily from tissue-specific differences in the relaxation times, $T_1$ (i.e., the time constant for the recovery of magnetization in the direction of the magnetic field) and $T_2$ (i.e., the time constant for the decay of magnetization in the plane perpendicular to the magnetic field). (For a review of MRI theory and applications see Gadian3).

These conventional MRI techniques include (i) $T_2$-weighted imaging, (ii) proton-density-weighted imaging, (iii) fluid-attenuated inversion-recovery imaging, (iv) standard $T_1$-weighted imaging, and (v) gadolinium-enhanced $T_2$-weighted imaging – each of which is described below. Figure 10-1 presents examples of images obtained using these techniques in patients with MS.

2.1. $T_2$-Weighted Imaging

MR images are $T_2$-weighted by allowing more time for signal decay to occur due to $T_2$ relaxation during a relatively-long echo time (TE). Signals from water protons located in tissues associated with longer $T_2$ values decay less during a long TE; because of this, such tissues appear hyperintense on $T_2$-weighted images relative to tissues with shorter $T_2$ values.

$T_2$ is prolonged in most pathologies that are associated with (i) inflammatory edema or tissue destruction (i.e., pathologies that increase bulk water that has less interaction with macromolecules) or (ii) gliosis in the white matter of the brain. For these reasons, MS lesions are hyperintense on $T_2$-weighted scans both in the early stages of the disease (i.e., when inflammation is most prominent) as well as in the later stages of the disease (i.e., when tissue injury and gliosis are more prominent).

2.1.1. $T_2$-Weighted Imaging of Multiple Sclerosis

Consistent with well-known pathological observations, the $T_2$-weighted MR appearance of MS (see Figure 10-1) is primarily one of multiple, hyperintense white-matter lesions with periventricular predominance37. (See Narayanan et al38 for an example of the probabilistic mapping of MS lesions). Because of their exquisite sensitivity to subtle changes in water, $T_2$-weighted hyperintensities can even identify regions of brain tissue that appear normal on gross pathology and that are only associated with a very subtle infiltration of inflammatory cells39.

2.1.1.1. Evolution of $T_2$-Weighted Hyperintense Lesions

New lesions that are seen on $T_2$-weighted imaging [or on proton-density-weighted imaging (see below)] have a characteristic evolution40. Typically, they reach a maximum size in approximately four weeks, decrease in size over the next six to eight weeks, and leave a residual $T_2$-weighted abnormality37 that is a permanent record of tissue injury5. For this reason, the total lesion volume that can be measured on such scans is often used as a surrogate measure of disease burden in MS. Furthermore, changes across time in the number and volume of lesions that are visible on $T_2$-weighted imaging can be used as indicators of disease activity and of response to treatment. It should be noted, however, that such changes in volume consist partly of inflammatory edema that eventually resolves with an associated decrease in the volume of $T_2$-weighted abnormality41.

2.1.1.2. Clinical Significance of $T_2$-Weighted Hyperintense Lesions

Although the relationship between $T_2$-weighted imaging abnormalities and abnormal findings on histological examination is strong37-39, the correlation between total cerebral $T_2$-weighted lesion load and clinical disability at any given time is only modest42,43. Nevertheless, the predictive value of $T_2$-weighted lesions for the future development of clinically-definite MS is strong – particularly over the long term. For example, Brex et al44 recently published the latest results of an ongoing, longitudinal study that had, at that point, followed a group of 71 patients for 14 years from the time of their initial episode of presumed CNS-demyelination. They found that clinically-definite MS eventually developed in 44 of the 50 patients with $T_2$-weighted lesions at presentation (but in only 4 of 21 patients that had presented with normal MRI). Furthermore, the number and the volume of $T_2$-weighted lesions at baseline, as well as the change in lesion volume over the first 5 years, correlated significantly with the patients’ degree of long-term disability as measured by the EDSS (i.e., Kurtzke’s Expanded Disability Status Scale45). The latter correlations were, however, of only moderate strength – suggesting that, on its own, $T_2$-weighted lesion data cannot be used to make strong predictions about the prognosis in a patient that is known to have MS.

The modest correlation seen between $T_2$-weighted lesion load and concurrent clinical disability may be explained by several factors: (i) the lack of pathological specificity of $T_2$-weighted abnormality, (ii) the fact that neurological disability is not easy to quantify and that the instruments used to do so (primarily the EDSS) are limited in their scope (e.g., the EDSS is based primarily on ambulatory ability), (iii) the fact that lesions in different CNS locations would be expected to correlate differently with disabilities in different spheres of CNS function (e.g., cerebral lesion-load is only weakly related to the sensorimotor dysfunction that results from spinal cord lesions – a dissociation that increases as the MS disease process progresses46), and (iv) the fact that lesions may not be the only pathology responsible for disability, particularly late in the disease when a neurodegenerative process may develop13. The correlation between $T_2$-weighted lesion volume and disability is also weakened by (v) the potential of the brain to functionally adapt to injury36,32-34 and (vi) the fact that focal lesions have diffuse consequences39,38. Thus, it is not surprising that it has been difficult to demonstrate a strong, direct effect of the localization of cerebral
T₂-weighted lesions on specific EDSS-measured functional impairments. Nevertheless, there are examples of specific functional deficits that have been shown to correlate with the T₂-weighted lesion load that is present in the region of the CNS associated with those particular functions (e.g., olfactory function, sustained complex-attention and verbal working-memory, and visual function).

**Centrum Semiovale**

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<th>T₂-weighted image</th>
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<th>T₁-weighted image</th>
<th>Gd-enhanced image</th>
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**Lateral Ventricles**

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<th>T₂-weighted image</th>
<th>PD-weighted image</th>
<th>T₁-weighted image</th>
<th>Gd-enhanced image</th>
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**Figure 10-1.** Cross-sectional slices through the centrum semiovale (top) and the lateral ventricles of a patient with multiple sclerosis (MS) as seen on T₂-weighted, proton-density-weighted (PD), T₁-weighted, and gadolinium-enhanced T₁-weighted images. Of note at the level of the centrum semiovale: (i) many of the hyperintense lesions that can be seen on the T₂- and PD-weighted images are also seen as hypointensities on the T₁-weighted images and (ii) two of these lesions are still active and inflammatory (as evidenced by the ring-like Gd-enhancement). Of note at the level of the lateral ventricles: (i) it is difficult to discriminate between the periventricular lesions and cerebrospinal fluid (CSF) on the T₂-weighted image, (ii) it is easy to discriminate between the periventricular lesions and the CSF on the PD-weighted image; (iii) the extent of T₂- and PD-weighted hyperintensity is much more extensive than the hypointensities seen on the T₁-weighted images; and (iii) there are no active, inflammatory lesions at this level (as evidenced by the lack of Gd-enhancement). (Images are courtesy of the Canadian MS/BMT Study Group).

### 2.1.1.3. T₂-Weighted Hypointensities

In addition to the T₂-weighted white-matter hyperintensities that we have dealt with thus far, grey-matter hypointensity on T₂-weighted imaging of patients with MS (which is thought to reflect pathologic iron deposition and brain degeneration) has also been described and shown to be related to clinical status and prognosis in MS.

### 2.2. Proton-Density-Weighted Imaging

Because both lesions and cerebrospinal fluid (CSF) are hyperintense on T₂-weighted images, the discrimination of periventricular lesions can be difficult. One way of increasing this discrimination is to acquire images with, so-called, “proton-density weighting.” Such images do not actually reflect the density of protons; they do, however, have intermediate T₁- (see below) and
T₂-weightings that, as shown in Figure 10-1, result in the CSF appearing dark (because its long T₁ value predominates over its long T₂) and lesions appearing bright (because their long T₂ values predominate over their relatively shorter T₁).

2.3. Fluid-Attenuated Inversion-Recovery Imaging

Another means of increasing contrast between CSF and lesions is through the use of fluid-attenuated inversion-recovery (FLAIR) images. This approach involves the use of an inversion pulse to suppress the signal arising from bulk water in the CSF. FLAIR images provide both (i) better discrimination between ventricular CSF and the periventricular T₂-weighted-hyperintensities that are associated with MS lesions and (ii) increased contrast for lesions – particularly for those that are cortical or juxtacortical.

2.4. T₁-Weighted Imaging

T₁-weighted images are produced by shortening the TR (i.e., the amount of time between successive repetitions of water-proton excitation) and, thereby, allowing less time for water to regain its equilibrium magnetization. Water protons in tissues with a relatively short T₁ recover more quickly and produce more signal at relatively-short TR than do those in tissues with a longer T₁. Protons in bulk water (e.g., in CSF, or in tissue that is associated with either extracellular edema or with a loss of structural integrity) have a long T₁ and, as shown in Figure 10-1, appear hypointense on T₁-weighted sequences.

T₁-weighted images are less sensitive to changes in either water-content or gliosis than are T₂-weighted images. Nevertheless, acute, inflammatory lesions can sometimes be associated with so much edema that they can show substantial T₁-weighted hypointensity. Chronic T₁-weighted hypointensities are, however, much more specific indicators of tissue destruction than are T₂-weighted hypointensities. The term “black hole” has been used to describe hypointense lesions on T₁-weighted images. Given the fact, however, that this term is typically used to imply an association with irreversible tissue destruction, use of the term is probably best reserved for lesions that are chronically-hypointense on T₁-weighted imaging. Only about 30% of new T₁-weighted lesions will evolve into chronic black holes.

2.4.1. T₁-Weighted Imaging of Multiple Sclerosis

Given the increased pathological specificity associated with T₁-weighted hypointensity, it is not surprising that lesions that show this feature on T₁-weighted imaging are more strongly correlated to disability in MS than are lesions that are T₁-isointense. In a recent study, Cid et al. examined the relationship between RR-MS patients’ (i) degree of lesion hypointensity on T₁-weighted imaging obtained at the time of an MS relapse, (ii) change in EDSS score between the time of the relapse and one month later, and (iii) amount of neuronal apoptosis induced on neuronal cultures by CSF obtained at the time of the relapse. They found a strong relationship between T₁-weighted lesion hypointensity and both (i) poor recovery from relapse and (ii) the amount of neuronal apoptosis induced by the CSF.

2.5. Gadolinium-Enhanced T₁-Weighted Imaging

As reviewed by Rovaris and Filippi, signal intensity on T₁-weighted imaging can be increased with the injection of a chelated form of gadolinium (Gd), which interacts with water so as to shorten its T₁ relaxation time. Normally, Gd does not cross the blood-brain barrier (BBB). However, focal inflammation in the CNS – as occurs during an MS attack – is often associated with an “opening” of the BBB. This opening allows Gd to pass through in a manner that is graded depending upon (i) the extent of the associated increase in BBB permeability, (ii) the dose of Gd administered, and (iii) the interval between Gd-injection and T₁-weighted MR acquisition (i.e., the time available for the Gd to leak across the BBB).

2.5.1. Gd-Enhanced T₁-Weighted Imaging of Multiple Sclerosis

The acute inflammatory process that was described above is transient. As a result, Gd only causes MS lesions to enhance for two to six weeks after they become detectable by conventional MRI. Thus, a useful role for Gd-enhanced T₁-weighted imaging is to help distinguish recently-appearing, inflammatory lesions from ones that are more chronic (and no longer associated with sufficient inflammation to result in Gd enhancement). Indeed, MRI assessment of disease activity in MS is often based upon the number of Gd-enhancing lesions that are seen within a T₁-weighted scan. The majority of enhancing lesions are “nodular,” but about 25% of lesions show “ring-like” enhancement. Such ring-enhancing lesions are associated with a more-severe clinical outcome and it has been suggested that they reflect a more-destructive pathology.

Most lesions that are Gd-enhancing on T₁-weighted images continue to be detectable on T₂-weighted images after the acute inflammation (and, thus, the Gd-enhancement) have resolved. Conversely, it is generally believed that (i) most T₂-weighted lesions in the central white matter of MS patients are associated with an initial, variable period of Gd-enhancement on T₁-weighted imaging and (ii) Gd-enhancing lesions and T₂-weighted lesions represent two different stages of a single pathological process. There is evidence, however, to suggest that some of the lesions on T₂-weighted images can develop independently of Gd-enhancement – perhaps because of (i) ongoing low-grade inflammation that is not detected with Gd-enhancement or (ii) mechanisms other than inflammation that are responsible for progression in some existing lesions.

2.5.1.1. Clinical Significance of Gd-Enhancement

About 50% of patients with MS will have at least one Gd-enhancing lesion at any given time. Surprisingly, in what is referred as the “clinico-radiological paradox,” a large proportion of these lesions are not associated with clinical manifestations: indeed, on average, Gd-enhancing lesions occur about ten times more frequently than clinical relapses. Despite the striking difference between the frequency of new Gd-enhancing lesions and the frequency of clinical exacerbations, there is still, however, a strong relationship between them. Furthermore, the number of enhancing lesions on a single scan is (i) predictive of subsequent relapse-rate and (ii) correlated with both subsequent enhancing-lesion activity and change in T₂-weighted lesion load.

Although the presence of one or more Gd-enhancing brain
lesions is predictive of conversion to clinically definite MS\textsuperscript{96}, Gd-enhancement is not a strong predictor of the development of cumulative impairment or EDSS-measured disability\textsuperscript{74}. These findings are consistent with the hypothesis that different pathogenetic mechanisms may be responsible for (i) the occurrence of relapses and (ii) the development of long-term disability.

3. NON-CONVENTIONAL MAGNETIC RESONANCE IMAGING TECHNIQUES

Even though the aforementioned conventional-MRI techniques have allowed us to image MS lesions with much greater sensitivity, these techniques are not capable of fully characterizing and quantifying the extent of tissue damage in patients with MS. A number of recently-developed MR techniques are better suited for such a role. These techniques include: (i) MTI, (ii) DWI, (iii) DTI, (iv) fMRI – each of which are, in turn, described below.

3.1. MAGNETIZATION-TRANSFER IMAGING

Protons associated with molecules that are large and less mobile than water (e.g., the macromolecules that make up cell membranes) have a very short T\textsubscript{2} and are not visible on conventional MRI; this is because their signals decay completely before conventional MRI data is acquired. The effect of these protons can, however, be observed indirectly by the phenomenon of magnetization transfer (MT)\textsuperscript{77}. In MTI, appropriate radio-frequency pulses are applied to selectively saturate the magnetization of the bound protons. This saturated magnetization is then naturally exchanged with those protons that are found in the relatively “mobile” protons of CSF, extracellular water, and intracellular water (i.e., the protons that are normally observed by MRI). This transfer of saturated magnetization to the MRI-observable, free-water pool results in a reduction of the signal intensity from the observable protons to a level below.

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An important advantage of MTI is that it can be easily quantified by calculating the magnetization-transfer ratio (MTR), which is the relative MRI signal intensity measured in the absence of a saturating pulse compared to the intensity that is measured in the presence of a saturating pulse (see Figure 10-2). A low MTR indicates less exchange of magnetization between tissue macromolecules and the surrounding water molecules.

![Figure 10-2](image-url)
before the appearance of lesions implies that MTI might provide information that could predict the future evolution of MS. This has led to the assessment of the predictive value of MTI in MS. For example, the prognostic value of MTI was recently examined by Santos et al., who found that mean NAWM-MTR values were able to successfully predict whether or not levels of disability would increase at five-year follow-up in patients with relatively-long-standing MS; importantly, MTR values within these individuals’ T2-weighted lesions could not predict such changes. In a related study of patients with a clinically-isolated syndrome suggestive of MS, Iannucci et al. found that MTR values at the time of presentation were significant predictors of the development of clinically-define MS within the next 25-42 months (although not as strong predictors as these patients’ presenting T2-weighted lesion volumes). On the other hand, Brex et al. found that mean NAWM-MTR values in a similar group of patients could not predict whether these individuals would go on to have MS in the following 12 months (at which point, these newly-diagnosed MS patients still had normal NAWM-MTR). Thus, while it is clear that MTI has prognostic value in MS, further studies are necessary to better characterize its strengths and limitations.

3.1.1.3. MTI of Normal-Appearing Grey Matter

As mentioned in the introduction, there is now an increasing appreciation that, at the microscopic level, there is substantial lesional pathology of the NAGM in patients with MS. The lesions in NAGM are associated with much less inflammation and demyelination than are the lesions in the white matter. Perhaps related to this, as well as to their size and to their location (i.e., adjacent to CSF), these lesions in the NAGM are largely undetected by current conventional MRI techniques. Thus, it is important that, in addition to the MTI changes in the lesonal and normal-appearing white matter of patients with MS, reductions in MTR values have also been found in the NAGM of patients with MS relative to normal controls. Together, these findings suggest that the pathological process that is at work in the brains of patients with MS is very diffuse and is not tissue-specific.

3.2. Diffusion-Weighted Imaging

As reviewed by Cercignani and Horsfield, DWI allows for the in vivo measurement of the diffusion of water in the CNS due to Brownian motion. Because both the axolemma and the myelin sheath restrict water diffusion in nerve fibers, pathological processes (such as those at work in MS) that modify the integrity of such tissues can result in a loss of restricting barriers and, thereby, increase the so-called “apparent diffusion coefficient” (ADC) of water.

The ADC is a measure of the random displacement of water molecules in a particular direction. Because of the restricting entities that are found in biological tissues, ADC values in the CNS are lower than the diffusion coefficient of pure water (hence the term “apparent diffusion coefficient of water”). A measure of diffusion that is independent of the orientation of structures is provided by the mean diffusivity index, D̄. Also referred to as the directionally-averaged ADC (or ADCavg), D̄ is the average of the ADCs measured in three orthogonal directions. (For a review of DWI theory and applications see, for example, Schaefer et al.)

As reviewed by Filippi and Inglese, the pathology associated with MS modifies the water self-diffusion characteristics in the CNS by altering the geometry and/or the permeability of structural barriers that are found therein. The application of DWI techniques to the study of MS is appealing in that they can provide a quantitative estimate of the degree of fiber disruption and, thus, potentially provide information on the mechanisms that lead to irreversible disability in this disease.

3.2.1. DWI of Multiple Sclerosis

DWI studies have consistently shown that the ADC of water is (i) higher in MS lesions than in NAWM (see Figure 10-3) and (ii) higher in acute lesions than in chronic lesions. Such studies have also consistently demonstrated that mean D̄ values are increased in the NAWM of MS patients compared to those observed in the white matter of healthy normal controls – a finding that hold true in the brain, the spinal cord, and the NAGM.

Figure 10-3. Cross-sectional slices through the lateral ventricles of a patient with multiple sclerosis as seen on proton-density-weighted (PD), diffusion-weighted, and diffusion-tensor imaging (which is reviewed in the next section). The asterisks point out the lesions that are seen as (i) hyperintensities on PD-weighted imaging, (ii) increased mean diffusivity (D̄) values on diffusion-weighted imaging, and (iii) decreased fractional anisotropy (FA) values on diffusion-tensor imaging. (Images are courtesy of J.S.W. Campbell).

D̄ values have been shown to correlate with individual MS patients’ EDSS scores and disease durations. Furthermore, D̄ values are higher in patients with SP-MS than in those with RR-MS and disease durations.

Interestingly, individual patients’ D̄ values are not significantly related to their MTR values and are only moderately related to decreases in their 1H-MRS-measured NA/Cr values (the relevance of which is explained in the section on 1H-MRS below). These findings suggest that MTI provides information about different aspects of brain pathology in MS than do these other two imaging techniques (i.e., MTI and 1H-MRS).
3.2.1.1 Temporal Evolution of Lesions on DWI

Serial DWI studies have also been used in order to investigate the changes in NAWM that precede the development of acute MS lesions. For example, Rocca et al.\(^1\) found that regions of NAWM that would subsequently become Gd-enhancing lesions had a significant increase in their mean \(\overline{D}\) values starting six weeks prior to the appearance of enhancement. Furthermore, Werring et al.\(^2\), who acquired a years’ worth of monthly DWI scans in MS patients, observed (i) a steady and moderate increase in mean NAWM \(\overline{D}\) values that was followed by (ii) a rapid and marked increase at the time of Gd-enhancement and (iii) a slow decay after the end of enhancement. These two studies suggest that new focal lesions that are associated with an eventual breakdown of the BBB are preceded by subtle, progressive alterations in tissue integrity that are below the resolution of conventional MRI. Interestingly, Werring et al.\(^2\) also found that there was a mild increase in the mean \(\overline{D}\) values of NAWM regions that were contralateral and homologous to the NAWM regions that evolved into Gd-enhancing lesions (but that themselves did not become lesional) – a finding that supports the concept that structural damage in lesions can cause disturbances in connected areas of NAWM.\(^3\).

3.3 Diffusion-Tensor Imaging

The ADC of water in biological tissue that has a regular and ordered microstructure depends upon the direction along which it is measured (i.e., it is anisotropic)\(^1\)\(^\text{103}\). Thus, \(\overline{D}\) (which has a magnitude but no direction) does not provide a complete description of the diffusion phenomenon. A full characterization can, however, be obtained in terms of a tensor (i.e., a matrix of numbers) that describes the diffusion of water in three dimensions. From such a tensor it is possible to derive an index of diffusion anisotropy – the most commonly-used index being that of fractional anisotropy (FA)\(^1\)\(^\text{123; 124}\). FA values obtained using DTI reflect the degree of cellular-structure alignment within the tissue that is being imaged.

In the normal brain, FA images show a marked difference between (i) grey matter and CSF (which are both virtually isotropic) and (ii) white matter (which has a variable degree of anisotropy)\(^1\)\(^\text{125}\). Maximum FA values are found in white-matter regions that are characterized by a strongly-ordered parallel arrangement of fibers, whereas much lower values are found in regions where white matter fibers have incoherent orientations or where fiber-bundles cross. In DTI voxels that are normally full of highly-ordered fibers, a relative decrease in diffusion anisotropy could signal structural disintegration within the CNS and could be used to detect both focal damage to major neuronal pathways as well as remote damage resulting from Wallerian degeneration\(^1\)\(^\text{126}\). It should be noted that DTI would be expected to be less sensitive to such damage in voxels that contained less-ordered tissue or that contained crossing fibers.

3.3.1 DTI of Multiple Sclerosis

Results similar to those found using DWI have also been found using DTI in patients with MS. For example, as shown in Figure 10-3, DTI measures of FA have been shown to be decreased in the NAWM of patients with MS\(^1\)\(^\text{18; 29; 126; 127}\) and to be even more decreased in lesions\(^1\)\(^\text{18; 126; 127}\) – the greatest FA decreases typically being found in the most destructive (i.e., T\(_1\)-weighted hypointense) lesions\(^1\)\(^\text{18; 126; 127}\). Similar to the \(\overline{D}\) findings described above\(^1\)\(^\text{109}\), there is also a lack of relationship between individual MS patients’ FA values and their MTR values\(^1\)\(^\text{128; 129}\) – further suggesting that diffusion imaging and MTI provide somewhat independent measures of brain pathology in MS. Interestingly, whereas significant negative relationships have been found between individuals’ EDSS scores and their FA values\(^1\)\(^\text{18; 29; 127}\), abnormalities in FA have not yet been found in RR-MS at the very early stages of their disease\(^1\)\(^\text{130}\) and mean FA difference have not yet been found between different MS subgroups\(^1\)\(^\text{18; 29}\). If this is not simply the result of a low sensitivity of DTI for detecting structural damage, this would imply that the disability in RR-MS has a basis more in dysfunction than in loss of structural integrity.

3.4 Proton Magnetic Resonance Spectroscopy

None of the water-based imaging methods that we have reviewed so far can provide pathological specificity for injury to a particular cell type. Pathological specificity for injury to neurons and neuronal processes (i.e., axons and dendrites) can, however, be provided by quantification of the neuronal marker compound, N-acetylaspartate (NAA) using\(^1\)\(^\text{1\text{H}}\)-MRS\(^1\)\(^\text{131}\).

\(^1\)H-MRS is fundamentally different from the water-proton-based MRI techniques that we have discussed thus far in that it records signals that arise from protons in metabolites that are present in brain tissue at concentrations approximately one thousand times lower than that of tissue water\(^1\)\(^\text{132}\). Whereas the signal-to-noise ratio and image resolution that is possible with these metabolite-based images is much lower than that for water-based images, the resulting images can provide chemico-pathological specificity that is not possible with conventional MR images. The various approaches to in vivo \(^1\)H-MRS include: (i) single-voxel \(^1\)H-MRS studies (in which proton spectra are acquired from a single volume) and (ii) \(^1\)H-MRS imaging (\(^1\)H-MRSI) studies (in which proton spectra are obtained from multiple volume elements (i.e., voxels) at the same time).

3.4.1.1 \(^1\)H-MRS Metabolites of Interest

As shown in Figure 10-4, the water-suppressed, localized \(^1\)H-MRS spectrum of the normal human brain that is recorded at relatively-long echo times (usually 136 - 272 ms) reveals three major resonance peaks [the locations of which are expressed as the difference in parts per million (ppm) between the resonance frequency of the compound of interest and that of a standard compound (i.e., tetramethylsilane)]. These peaks are commonly ascribed to the following metabolites: (i) tetramethyl amines (Cho), which resonate at 3.2 ppm and are mostly choline-containing phospholipids that participate in membrane synthesis and degradation; (ii) creatine and phosphocreatine (Cr), which resonate at 3.0 ppm and play an important role in energy metabolism; and (iii) N-acetyl groups (NA), which resonate at 2.0 ppm and are comprised primarily of the neurally-localized NAA. A fourth peak usually arising from either the methyl resonance of lactate (La) or lipids (which both resonate at 1.3 ppm), is normally only barely visible above the baseline noise but can be detected in certain pathological conditions. Spectra acquired at shorter echo times (e.g., 30 ms) are better for detecting resonances that have a short T\(_2\) (e.g.,

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\(^1\)H-MRS imaging (\(^1\)H-MRSI) studies [in which proton spectra are obtained from multiple volume elements (i.e., voxels) at the same time].
lips and inositol). Unfortunately, such short-\(T_2\) \(1\)H-MRS records broad, overlapping signals that complicate the quantification of such spectra.

**Figure 10-4.** Proton-density-weighted magnetic resonance images through the centrum semiovale and the results of proton magnetic resonance spectroscopic imaging \((1\)H-MRSI) in a normal control subject and in a patient with multiple sclerosis. The superimposed grid in each image represents individual \(1\)H-MRSI voxels, and the large, thick, white box represents the entire \(1\)H-MRSI volume of interest for that individual. The smaller, numbered boxes represent voxels of normal-appearing white matter (NAWM) and lesional brain tissue in the patient and normal white matter (NWM) in the normal control subject. The \(1\)H-MRSI spectra from within each of these voxels is shown to the right of each image. The areas under the NA and Cho peaks (normalized to Cr) are shown above each spectrum. The spectra have been scaled so that the Cr peak in each of them has the same height. Note (i) the decrease in NA/Cr values from the patient’s NAWM voxel relative to the NWM voxels in the control subject, (ii) the even greater decrease in lesional NA/Cr, and (iii) the increased Cho/Cr in the patient’s NAWM voxel, which may be predictive of a soon-to-appear lesion in that location.

The simplest approach to the quantitation of \(1\)H-MR spectra is to normalize the NA and Cho signal intensities to the signal intensity from Cr in the same voxel\(^{131}\). Of course, this latter method does not provide absolute quantification and, importantly, the resulting measures of relative concentration are only valid if the underlying pathology does not substantially affect the local concentration of Cr. Thus, it is important that Cr concentrations are relatively constant throughout normal brain tissue and that they have also been shown to be relatively constant in both the lesions\(^{133, 134}\) and the NAWM\(^{134, 136}\) of patients with MS. It should be noted, however, that Cr values have been shown to decrease in acute\(^{133}\) and severely-hypointense lesions\(^{136}\); thus, it is inappropriate to normalize within-lesion NA and Cho values to within-lesion Cr values in either acute lesions or \(T_1\)-weighted black holes.

The limitations of ratio-based quantitation can be overcome by the various methods of semi-absolute quantification that have been developed\(^{137, 138}\). Unfortunately, such methods have their own limitations; for example, (i) they are dependent on many assumptions, (ii) they can be difficult to carry out, and (iii) they tend to have more variance than those based on ratios.

### 3.4.2. \(1\)H-MRS of Multiple Sclerosis

The resonance intensity that is ascribed to NAA is, arguably, the most important \(1\)H-MRS signal in the characterization of MS pathology because NAA is localized exclusively within neurons and neuronal processes such as axons and dendrites\(^{139, 140}\). Although NAA has been found in cell cultures of oligodendroglial cell lineage\(^{131, 142}\), this appears to be a phenomenon that is limited to cell cultures. Indeed, the specificity of NAA as an axon-specific marker \textit{in vivo}, even in the presence of injury and significant density of oligodendroglial cell precursors, has been confirmed in a recent biochemical and immunohistochemical study of rat optic nerve transection\(^{143}\). Furthermore, the validity of NAA as a surrogate for axonal density in MS has been confirmed in studies that correlated (i) findings from \textit{in vivo} \(1\)H-MRSI and histopathological analysis of cerebral biopsy specimens\(^{144}\) and (ii) findings from HPLC and histopathological analysis of spinal cord biopsy specimens\(^{145}\).

### 3.4.2.1. NA/Cr

\(1\)H-MRSI-measured NA/Cr values have been used to quantify neuronal and axonal integrity \textit{in vivo} in the brains of patients with MS for over a decade now\(^{146, 147}\). \(1\)H-MRS studies have shown that periventricular NA/Cr values are low in both the lesions and, to a lesser extent, the NAWM of patients with MS\(^{9, 122, 147, 148}\). Patients with SP-MS are more affected than those with RR-MS\(^{9, 149}\).

Interestingly, however, this latter finding seems to be related more to NA/Cr differences in NAWM than in lesions\(^{19}\). Importantly, just as with MTI and DWI, \(1\)H-MRSI-measured values of NA/Cr within the cortical NAGM of patients with MS have also been shown to be decreased relative to those in the cortical grey matter of healthy normal controls\(^{30, 31}\).

Decreases in MS patients’ periventricular-NA/Cr values are strongly related to both their disease duration and their EDSS scores\(^{149}\). Importantly, the correlation between patients’ EDSS scores and their periventricular NA/Cr values is as strong, or stronger, than that of any other MRI measure\(^{150}\) – a relationship that becomes even stronger when EDSS scores are correlated with estimates of NA/Cr in pure periventricular NAWM\(^{19, 20}\). In addition to correlating with patient’s EDSS scores (which are greatly influenced by a patients’ ambulatory status), periventricular-NA/Cr values in MS patients have also been shown to be strongly related to their cognitive abilities\(^{151}\).

### 3.4.2.2. Other Metabolites

In addition to NA, several other \(1\)H-MRS resonance intensities are also important in understanding the MS disease process. For example, \(1\)H-MRS-observed Cho and lipid peaks are thought to provide important information regarding myelin breakdown in the MS disease process\(^{33, 148}\). Furthermore, the presence of myo-inositol has been proposed as a marker of glial cells and gliosis\(^{30}\).

### 3.4.2.3. Temporal Evolution of Lesions on \(1\)H-MRS

As with MTI and DWI, the earliest abnormalities that are visible on \(1\)H-MRS occur months before the appearance of Ge-enhanced or \(T_2\)-weighted lesions. For example, regions of NAWM that will go on to become lesions have been shown to be associated with locally-increased levels of both Cho\(^{24}\) and lipids\(^{23}\) – both of which are markers of abnormality in cell membranes. As newly-
developing lesions become detectable on conventional MRI, they are associated with focal inflammation, demyelination, and axonal injury – pathological processes that result in decreases to NA/Cr values\(^{148, 152-154}\), further increases to Cho/Cr values\(^{148, 152-154}\), and acutely-increased LA/Cr values\(^{148}\).

Importantly, these NA-related decreases may persist chronically – particularly in the core of chronic lesions\(^{148}\). On the other hand, the presence of LA is more common in lesions that are Gd-enhancing\(^{150}\) and seems to resolve within weeks\(^{148}\). Increases in Cho/Cr are pronounced in Gd-enhancing lesions\(^{153, 154}\) and may remain elevated for years\(^{148}\), but eventually return to normal\(^{136, 148}\).

3.4.2.4. Spatial Distribution of \(^1\)H-MRCSI Pathology

Changes in \(^1\)H-MRCSI metabolites are greatest in the core of lesions and decrease with increasing distance from their center\(^{148}\). Importantly, they do not end at the edge of the T\(_2\)-weighted abnormality but extend into the surrounding NAWM\(^{148}\). For example, in the hyper-acute phase of the lesion (i.e., when it is still expanding), both the decrease in NA/Cr and the increase in Cho/Cr can be found around the lesion in the NAWM that is well beyond the expanding T\(_2\)-weighted abnormality. It is still not clear if the NAWM abnormalities in patients with MS result from (i) the sum of the remote effects of focal, lesional pathology or (ii) an independent process that is more diffuse.

3.5. Functional Magnetic Resonance Imaging

fMRI is another MR technique that differs fundamentally from the others discussed so far. For example, the blood-oxygen level dependent method of fMRI (a widely-used approach to such an analysis) exploits the fact that hemoglobin and deoxyhemoglobin are magnetically different such that hemoglobin shows up better on MRI images than does deoxyhemoglobin\(^{155}\). Brain activation is associated with increased blood flow and greater blood oxygenation that, in turn, produce an increased MR signal. fMRI involves (i) the acquisition of a series of such MR images of the brain in quick succession and (ii) the statistical analysis of these images in order to quantify subtle changes in the functional state of the brain across time.

3.5.1. fMRI of Multiple Sclerosis

Thus far, fMRI has been used in patients with MS to study abnormal patterns of brain activation that occur during the performance of simple motor tasks\(^{20, 32-34, 156, 157}\). These studies have shown that, as with other forms of brain injury, there is adaptive cortical reorganization in patients with MS as evidenced by extended, bilateral activation in motor-related regions (as opposed to the more-constrained, mostly-unilateral activation that is seen in normal controls during the tasks that have been used in these studies).

Reddy et al\(^{156}\) combined findings from fMRI of a simple finger-flexion task with those from \(^1\)H-MRCSI. As shown in Figure 10-5, they demonstrated that the extent of this functional reorganization [as expressed in the form of a lateralization index (LI) that reflected the degree of bilateral versus unilateral functional-activation] was strongly related to the presence of axonal injury (as measured by decreased periventricular NA/Cr on \(^1\)H-MRCSI). LI values have since been shown to be even more related to FA and NA/Cr values that are measured specifically within the periventricular NAWM\(^{20}\) – implying that NAWM changes are more specifically related to functional change than those in non-segmented periventricular brain tissue (which contains NAWM, NAGM, and lesions). This re-organized cortico-motor activation has been found in regions of the brain that are usually only activated in the execution of more-complex motor tasks – suggesting that such activation reflects, at least in part, disinhibition of latent motor pathways that are “recruited” to limit any functional impairment related to the tissue damage associated with MS\(^{57}\). Individual patients’ levels of activation within these recruited areas have been shown to be related to their (i) EDSS scores, (ii) disease duration, (iii) extent and number of spinal cord lesions, (iv) brain and spinal-cord MTR, (v) whole-brain \(T_2\), and (vi) whole-brain FA\(^{157}\). Together, these findings suggest that compensation due to adaptive cortical changes can contribute to sustaining motor functions during the early stages of MS; as a result, the actual extent of cortico-functional pathology in patients with MS may be greater than that which is clinically evident.

![Figure 10-5. Examples of fMRI activation maps (in white) obtained during a simple finger-flexion motor task and registered on to anatomical MR images for a normal control subject, a multiple sclerosis (MS) patient with normal periventricular NA/Cr, and an MS patient with abnormally-low periventricular NA/Cr. Both patients were able to perform the task without difficulty and had low disability ratings. Note the larger, bilateral extent of functional activation in the patient with low NA/Cr. (Images are courtesy of Dr. P.M. Matthews).](image)

4. MR-Based Assessment of Brain Atrophy

Atrophy of the brain or spinal cord at post mortem examination is one of the pathological hallmarks of irreversible CNS damage. As reviewed by Simon\(^{35}\), with the advent of MRI, it is now possible to assess CNS atrophy in vivo using a variety of measures that include, for example, (i) ventricular enlargement, (ii) grey- and white-matter volumes, and (iii) the use of more-global measures such as (a) the brain parenchymal fraction (BPF, i.e., the ratio of brain parenchymal volume to the total volume within the surface contour of the brain)\(^{158}\) or (b) BICCR (i.e., the ratio of brain parenchymal volume within the surface contour of the inner table of the skull)\(^{159}\).
4.1. Atrophy in Multiple Sclerosis

CNS atrophy in patients with MS has been documented since the original autopsy examinations of such individuals – with atrophy having been shown to reflect (i) injury and loss of both (a) neurons and their processes and (b) oligodendrocytes and the myelin that they produce, as well as (ii) changes in the supporting matrix that result from the contraction of glial tissue. Until recently, such atrophy has generally been thought of as occurring late in the disease; this view has changed, however, with the development of neuroimaging techniques that have demonstrating atrophy in the majority of patients with MS – even at very early stages of the disease.

4.1.1. Clinical Significance of CNS Atrophy

The average amount of accumulated spinal cord atrophy has been shown to be greater in patients with SP-MS than in patients with RR disease. Similarly, as a group, SP-MS patients have also been shown to have smaller brain volumes, and larger lateral ventricles, than RR-MS patients (see Figure 10-6).

![Figure 10-6. Cross-sectional slices through the lateral ventricles of a normal control subject, a patient with relapsing-remitting multiple sclerosis (RR-MS), and a patient with secondary-progressive multiple sclerosis (SP-MS) as seen on T2-weighted imaging. Note (i) the high degree of atrophy seen even in the early stage of the disease (as evidenced visually by the ventricular enlargement in the RR-MS patient as compared to the control subject) and (ii) the even-greater degree of atrophy that is seen in the secondary-progressive stage of the disease (as evidenced visually by the sulcal enlargement, the decreased volume of the white- and grey-matter, and the further-increased ventricular enlargement in the SP-MS patient).](image)

Brainstem and upper-spinal-cord atrophy have been shown to be strongly correlated with EDSS scores in patients with MS. This may, in part, be due to the fact that atrophy in these regions can be related to Wallerian degeneration following damage to the cerebrum, to the spinal cord, or to both. Moderate correlations have also been found between individuals’ EDSS scores and their degrees of (i) callosal atrophy, (ii) cerebral white-matter atrophy, and (iii) ventricular enlargement. On the other hand, correlations between EDSS scores and brain-parenchyma-based estimates of atrophy have been variable – ranging from strong to non-significant. It should be noted that MRI measures of brain volume and atrophy have been also shown to be significantly related to the presence of depression, impaired quality of life, and cognitive decline in patients with MS.

4.1.1.2. Rate of Atrophy

Brain atrophy develops at a remarkably-high rate in patients with MS. For instance, Fox et al. showed that (i) the yearly rate of cerebral atrophy in their MS group (0.8% per year) was over twice that of normal controls (0.3%) and (ii) the yearly rate of ventricular enlargement in patients was almost five times greater than in the controls (1.6 versus 0.3 cc per year). Furthermore, Simon et al. studied 85 RR-MS patients with mild-to-moderate disability over the course of two years and found that (i) the volume of the lateral ventricles increased at a rate of 5.5% per year and (ii) the area of the corpus callosum decreased at a rate of 4.9% per year. The course of cerebral atrophy in these patients was related to prior inflammatory disease activity as indicated by the presence of Gd-enhancing, T2-weighted lesions at baseline. Analysis of a subset of these patients (n=72) found a yearly decrease of 0.61% in their BPF, which translated to a yearly loss of approximately 8 cc per year.

There is some preliminary evidence to suggest that the rate of atrophy in patients with RR-MS differs from that in patients with SP-MS in a region-specific manner. For example, SP-MS patients seem to have a significantly-faster rate of atrophy around the ventricles than patients with RR-MS – suggesting a greater relative volume change along the long projection tracts. On the other hand, the rate of spinal cord atrophy has been reported to be faster in patients with RR-MS. These findings suggest that CNS atrophy may not be a uniform process and that different regions may have distinct responses to disease progression.

4.1.1.3. Relationship of Atrophy to Other MRI Measures

As might be expected, CNS atrophy in patients with MS has been shown to be related to many of the other MRI-measures that we have reviewed in this chapter. For example, patients’ supratentorial brain volumes have been shown to be significantly related to their load of hypointense lesions on T2-weighted imaging. Similarly, patients’ numbers of Gd-enhancing T2-weighted lesions have been shown to be well-correlated with an increase in their ventricular size – especially in patients with a high proportion of ring-enhancing lesions. Furthermore, in two related longitudinal studies, Lukas et al. found that patients’ total numbers of new Gd-enhancing lesions were related to their monthly changes in ventricular volume, and Simon et al. found that the degree of cerebral atrophy observed over a two-year period (as indicated by ventricular enlargement and callosal atrophy) was greater for patients that had entered their trial with Gd-enhancing lesions. It should be noted, however, that not all studies have found a relationship between Gd-enhancement and atrophy.

The relationship of atrophy with T2-weighted lesion load has also been somewhat inconsistent. For example, whereas some groups have found a significant relationship between their patients’ T2-hyperintense lesion load and their degree of ventricular enlargement, others have been unable to find a significant relationship with their patients’ supratentorial brain volumes.

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The relationship between cerebral atrophy and the newer, non-conventional MRI measures seems to be more consistent. For example, brain volume has been shown to correlate with both (i) MTR values within normal-appearing brain tissue\(^{18}\) and (ii) \(D\) values within the brain parenchyma\(^{15}\). Furthermore, Collins et al\(^{15}\) found that cerebral atrophy (as measured by BICCR values) was correlated with periventricular axonal injury (as measured by decreases in \(^{1}H\)-MRSI NA/Cr values) in their group of patients with SP-MS. BICCR values in their group of mildly-disabled patients with RR-MS were not reduced relative to their normal control group, even though this group of patients did have significantly reduced NA/Cr values. Together, these findings suggest that microscopic and biochemical changes in the brains of patients with MS are related to the decreases in brain volume that are found in such individuals; importantly, however, there seems to be a decoupling between axonal damage and atrophy in the very early stages of the disease.

### Caveats

It should be noted that current MRI analysis techniques allow for the measurement of small changes in volume on the order of 0.2% of total brain volume – changes of magnitude that are much smaller than those that can be identified on gross pathological examination. Thus far, it has been tempting to (i) assume that these small changes in brain volume have the same pathological significance as gross atrophy post mortem and (ii) suggest that they provide a measure of a specific pathological feature such as axonal loss. Unfortunately, it is not clear that this is always the case: for example, myelin loss, glial- and matrix-related changes, as well as shifts in water distribution all occur in MS and may be associated with volume changes of this magnitude. Although it is clear that volume measurements must contribute in some way to estimating the full extent of irreversible axonal damage in MS, further investigations are required to understand the precise pathological significance of atrophy and the mechanisms that contribute to its progression.

### 5. SUMMARY AND CONCLUSIONS

As we have seen, our understanding of the pathology and pathophysiology of MS has been greatly advanced by information obtained using MRI. For example, the conventional MRI techniques that were described above have greatly increased the sensitivity with which lesions can be detected. In addition, they have also provided us with a great deal of \textit{in vivo} information regarding the spatial distribution, temporal dynamics, and clinical significance of these lesions. Furthermore, the newer, non-conventional methods of MR acquisition and analysis that were also described above have allowed us to quantify \textit{in vivo} the microscopic, molecular pathology; the biochemical changes; the cortico-functional adaptations; and the progressive atrophy that may occur in the brain and spinal cord of patients with MS.

Based primarily on the findings from the non-conventional MRI methods that were reviewed in this chapter, a number of important insights regarding MS pathology and pathophysiology have become evident. First, there are significant pathological changes in the otherwise normal-appearing grey and white matter of patients with MS, consistent with the emerging view that the pathology in this disease is relatively diffuse and not specifically tied to the white matter. Importantly, the amount of such microscopic, pathological change in any individual patient is highly related to their degree of concurrent disability and is also related to future changes in their disability. Second, certain pathological changes in NAWM can foreshadow the appearance of the focal lesions that are classically associated with MS. Third, there is significant cortico-functional reorganization that takes place in the brains of patients with MS; a reorganization that, at least at the early stages of the disease, seems to have the potential to be functionally-adaptive and compensate for some of the effects of the ongoing neuropathological processes that are associated with the disease. Fourth, all of these changes are occurring in parallel with the progressive CNS atrophy, even in the early course of the disease.

Although findings from MRI have taught us much about the MS disease process over the sixteen years since the publication of the first edition of this volume, we still have much to learn about the spatial and temporal dynamics of the lesional and non-lesional pathological tissue that characterizes the MS brain. It is the hope and goal of the present authors that a multimodal, multiparametric approach to the analysis of longitudinal data obtained from a combination of conventional and non-conventional imaging techniques will become commonplace. Such an approach still has much to teach us about the spatial and temporal characteristics of the MS disease process, and the knowledge that it will provide us with will undoubtedly lead to better methods of treating and monitoring MS.

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