Introduction

Conventional magnetic resonance imaging (MRI) is widely used for the diagnosis and monitoring of multiple sclerosis (MS), because it is more sensitive than clinical assessment in detecting disease dissemination over space and time [1] and for revealing the occurrence of disease activity and the accumulation of disease burden over time. Nevertheless, the discrepancies between clinical and conventional MRI findings in patients with established MS [2] highlight the fact that conventional MRI is unable to reliably assess the more disabling pathological features of the disease, including axonal and neuronal loss.

During the last decade, diffusion-weighted imaging (DWI) is increasingly being applied to the study of MS, because of its ability to detect and quantify disease-related changes in the tissue microstructure within and outside T2-visible lesions. Since diffusion can be defined as the microscopic random translational motion of molecules in a fluid system, in the central nervous system (CNS), this parameter is influenced by several tissue components, including cell membranes and organelles. The MRI-measured diffusion coefficient of healthy biological tissues is, therefore, lower than that in free water and is called the apparent diffusion coefficient (ADC) [3]. Pathological processes which result in a loss or increased permeability of “restricting” barriers can determine an increase in the ADC values. Since the magnitude of diffusion is dependent on the direction in which it is measured, DWI can also give information about the geometry of tissue structures [4]. A full characterization of diffusion can be obtained in terms of a tensor [5], a $3 \times 3$ matrix which accounts for the correlation existing between molecular displacement along orthogonal directions. From the tensor, it is possible to derive the mean diffusivity (MD), which is a measure of diffusivity independent of the spatial orientation of tissue structures, and some other dimensionless indices of anisotropic diffusion, including fractional anisotropy (FA) [6, 7], which reflect the prevalence of diffusivity along one spatial direction (e.g., along axonal fibers rather than perpendicular to them). Against this background, the pieces of evidence supporting a role for DWI in the study of neurodegeneration in MS and in monitoring its evolution over time will be reviewed critically.
DWI and Neurodegeneration in MS

Pathological Specificity

In principle, both demyelination and axonal degeneration have the potential to alter the permeability or geometry of structural barriers to water molecular diffusion in the brain, thus leading to DWI-detectable changes. A high-field ex vivo DWI study of post-mortem MS spinal cord (four cases) has revealed abnormalities of ADC and an index of anisotropy when compared with one healthy control sample [8]. The anisotropy measure provided a better correlation with axonal density ($r=0.61$, $p<0.001$) and myelin content ($r=0.51$, $p<0.001$) than did ADC ($r=-0.32$, $p=0.017$ and $r=-0.45$, $p=0.001$, respectively). Moreover, the results of DWI studies of aging [9] and Alzheimer’s disease [10, 11] also support the notion that this technique has the potential to quantify the severity of degenerative changes in the human brain.

The pathological specificity of DWI for neurodegeneration is also highlighted by the available studies of T2-visible MS lesions [12-24] (Fig. 1). Despite always

![Fig. 1. Axial proton density-weighted spin-echo image (A), MD map (B), and FA map (C) from the brain of a patient with CIS suggestive of MS at the level of the lateral ventricles. The patient fulfilled MRI criteria for disease dissemination in space. Within the white circle, one periventricular, hyperintense lesion is visible in a. Diffusivity is increased within this lesion, which also appears hyperintense on the MD map in b. Conversely, this lesion is visible as an area of decreased signal on the FA map in c, indicating a local decrease of tissue anisotropic diffusion (Reproduced with permission from [31])](image)