Advanced magnetic resonance imaging techniques to better understand multiple sclerosis

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Abstract Magnetic resonance imaging (MRI) has considerably improved the diagnosis and monitoring of multiple sclerosis (MS). Conventional MRI such as T₂-weighted and gadolinium-enhanced T₁-weighted sequences detect focal lesions of the white matter, damage of the blood–brain barrier, and tissue loss and inflammatory activity within lesions. However, these conventional MRI metrics lack the specificity required for characterizing the underlying pathophysiology, especially diffuse damage occurring throughout the whole central nervous system. To overcome these limitations, advanced MRI techniques have been developed to get more sensitive and specific parameters of focal and diffuse brain damage. Among these techniques, magnetization transfer imaging, diffusion MRI, functional MRI, and magnetic resonance spectroscopy are the most significant. In this article, we provide an overview of these advanced MRI techniques and their contribution to the better characterization and understanding of MS.

Keywords Multiple sclerosis · MRI · Magnetization transfer imaging · Diffusion MRI · Functional MRI · MR spectroscopy

Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS) representing the leading cause of neurological disability in young adults (Miller 2004). Focal inflammatory and demyelinating lesions disseminated in white matter have been considered during several decades as the main feature of MS. However, recent histological studies confirming the original observations by Charcot (Charcot 1868) have also evidenced the presence of diffuse and progressive damage in cerebral white matter (WM) and gray matter (GM) (Kutzelnigg et al. 2005; Lassmann et al. 2007). These pathological processes mainly include diffuse inflammation, global brain atrophy, and axonal loss.

Conventional magnetic resonance imaging (MRI) techniques (Hornak 2010) are powerful tools to detect focal MS lesions. T₂-weighted sequences, T₁-weighted sequences, and gadolinium-enhanced T₁-weighted sequences are sensitive to detect focal demyelinating lesions of the white matter, damage of the blood–brain barrier, and tissue loss and inflammatory activity within lesions (Neema et al. 2007; Rovira and Leon 2008) (Fig. 1). However, conventional MRI suffers from a main drawback. Its low specificity limits the ability to assess the entire spectrum of the pathophysiological processes occurring throughout the whole CNS and especially the diffuse damage within WM and GM that are thought to be the major substrate leading to irreversible disability in MS (Neema et al. 2007). To overcome these limitations, advanced MRI techniques have been developed or optimized to better characterize the underlying pathophysiology of the disease (Tofts 2003). Among the advanced techniques, magnetization transfer imaging, diffusion MRI, functional MRI, and MR spectroscopy have evidenced their ability to detect and monitor

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Fig. 1 Conventional T₂-weighted (a) and T₁-weighted post-gadolinium (b) images from a patient with early MS. Arrow indicates an acute inflammatory demyelinating lesion

diffuse damage in WM and GM by depicting subtle changes at the structural, functional, and metabolic levels.

The objective of this review is to provide an overview of these advanced quantitative MRI techniques that can help with a better understanding of the pathophysiological processes defining MS by monitoring the evolution of the disease.

Magnetization transfer imaging

Magnetization transfer imaging (MTI) is an advanced MRI technique that studies the integrity of the macromolecular environment that is not directly visible using conventional MRI techniques. The magnetization transfer contrast is based on the magnetic interactions and chemical exchanges between protons of free water and those bound to macromolecules. These exchanges can be detected by applying a radiofrequency pulse that selectively saturates the signal of bound protons, and by observing the variation on the signal intensity of water protons (Henkelman et al. 2001). The variation observed is proportional to the degree of exchange between the two pools and is quantified by the magnetization transfer ratio (MTR). Therefore, MTR reflects the integrity of macromolecular tissues like myelin (Grossman 1994; Dousset et al. 1998). MTR can be evaluated in regions of interest or in the whole brain using voxel-based analysis (Ranjeva et al. 2005).

Low MTR is an indicator of demyelination and axonal loss although this reduction may also be influenced by inflammation, gliosis, or edema (Rovira et al. 1999). A reduced MTR has been evidenced in focal acute and chronic MS lesions (Fig. 2). Newly appearing gadolinium-enhancing lesions tend to have initially low MTR which in time can partially or totally recover after restoration of the

blood–brain barrier integrity (Silver et al. 1998) depending on the efficiency of the repaired tissue process. MTR recovery probably reflects remyelination or resorption of edema and inflammation.

Apart from the focal lesions, decreased MTR has also been observed in normal-appearing WM and GM tissues. The microscopic diffuse damage may appear very early in the course of the disease (Audoin et al. 2007a) and is more severe in progressive forms of MS (Sharma et al. 2006). MTR changes in normal-appearing WM and GM present moderate to strong correlations with physical disability (Iannucci et al. 1999; Khaleeli et al. 2007) and cognitive dysfunction (Filippi et al. 2000; Ranjeva et al. 2005). Data

Fig. 2 MTR map from a patient with early MS. Note that the MS lesion (arrow) presents a very low signal demonstrating a low MTR value

from several longitudinal studies (Agosta et al. 2006; Khaleeli et al. 2007) suggest that MTR may be a sensitive marker for predicting subsequent disability and disease progression.

Voxel-based analyses of MTR abnormalities allow better evaluation of the extent of macro- and micro-structural tissue damage in GM and WM of MS patients, the impact of local injury on cognitive performances, at the group level and even in the individual case (Ranjeva et al. 2005; Dwyer et al. 2009; Reuter et al. 2009).

Diffusion MRI

Diffusion imaging is an advanced MRI technique that studies the water diffusivity in brain tissues by assessing the microscopic Brownian motion of water molecules. This motion is influenced by the size, orientation, and structure of the surrounding tissues (cellular membranes, macromolecules, fibers). Therefore, diffusion MRI including diffusion-weighted MRI and diffusion tensor imaging (DTI) techniques provide indirect information about the integrity of the microstructure (Basser and Pierpaoli 1996; Beaulieu 2002).

To sensitize the MRI signal to diffusion, a pair of strong magnetic field gradients has to be applied in different directions within the MRI sequence (Stejskal and Tanner 1965). The first gradient pulse dephases the spins while the second rephases them if no net movement occurs. However, if net movement of spins occurs between the gradient pulses, signal attenuation occurs. The degree of attenuation depends on the magnitude of molecular translation. Therefore, in a cerebral region with high diffusion as in the cerebrospinal fluid, the corresponding signal on the diffusion-weighted image is low. Diffusion can be restricted in highly organized tissues that create obstacles that orientate the motion of the water molecules. For example, along axon fibers or myelin membranes, water diffusion is preponderant in the direction parallel to the orientation of the structure and is very limited in the perpendicular directions (Basser and Pierpaoli 1996). Among the diffusion MRI parameters, the apparent diffusion coefficient (ADC), a measure of the average molecular motion and fractional anisotropy (FA), a measure of the directional preponderance of diffusion can be assessed for each pixel (Fig. 3). With the diffusion tensor MRI technique, multiplication of the directions sensitized to diffusion, at least six to calculate a tensor, can be applied to describe the 3-dimensional shape of diffusion. Specific structures characterized by an equivalent orientation can be detected like nervous fibers or white matter tracts. Application of mathematical algorithms can be used to assess the probability of connection between the different brain areas. Then, the route of white matter tracts

can be computed and visualized (Mori and van Zijl 2002; Audoin et al. 2007b).

Focal MS lesions are generally characterized by increased ADC and decreased FA. However, a transient decrease in ADC values may occur in acute MS lesions. This pattern may reflect swelling of the myelin sheaths, reduced vascular supply leading to cytotoxic edema, or significant inflammatory cell infiltration (Rovira et al. 1999). In a study performed on postmortem tissues of progressive MS forms, Schmierer et al. (2007) demonstrated that mean diffusivity and fractional anisotropy correlated strongly with the myelin content and less strongly to axonal loss. Nevertheless, diffusion MRI metrics changes observed in vivo in focal MS lesions can also reflect inflammation, edema, and, to a lesser extent, gliosis. Moreover, in pure model of demyelination-remyelination induced in rodents, Song et al. (2005) demonstrated that reduced FA during demyelination is related to variation in radial diffusivity (diffusion perpendicular to the main diffusion direction of water in the tissue), a parameter highly sensitive to demyelination, relative to longitudinal diffusivity, a parameter more related to axonal loss.

Diffuse tissue damage has been demonstrated by diffusion MRI in normal appearing WM and GM with, in addition, an overall increase in ADC and a decrease of FA (Werring et al. 2000; Ceccarelli et al. 2007). These data suggest the presence of subtle microstructural injuries that are not visible in conventional MRI.

The overall WM and GM diffusion changes have been found to contribute to the development of clinical deficits and to predict accumulation of disability (Rovaris et al. 2005).

Functional MRI

Functional MRI (fMRI) is an advanced MRI technique based on the blood oxygen level-dependent (BOLD) effect (Kwong et al. 1992). fMRI is an indirect method that studies brain activity by detecting the transient hemodynamical response provoked by neuronal activity that induces an increase in oxygen consumption and an even higher increase in local blood flow (neurovascular coupling) (Ogawa et al. 1990). As the increase in flow exceeds the increase in oxygen consumption, neuronal activity is expressed as a relative increase in oxyhemoglobin compared to deoxyhemoglobin in the activated cerebral zones. The relative decrease in deoxyhemoglobin concentration, which has a paramagnetic effect, can be detected by MRI as a weak transient rise in the T_2^* -weighted signal. This is the BOLD contrast.

fMRI is useful to assess brain areas involved in the achievement of a simple motor task like movement of the

Fig. 3 Diffusion imaging including ADC map (a), FA map (b), and diffusion tensor tracking image (c) from a patient with early MS. Note that the MS lesion (arrow) presents abnormal diffusion contrasts compared to normal appearing tissue

hand (Fig. 4) or a complex cognitive task like the realization of neuropsychological tests adapted to performance within the MRI scanner.

In MS, fMRI has been defined as a powerful tool to point out brain functional reorganization that begins from the earliest stages of the disease. To achieve a specific task, patients compared to healthy controls have to recruit brain areas known to be involved in the realization of more complex tasks. These compensatory processes are detected within the motor system, the visual system, or high level cognitive systems (Rocca and Filippi 2007). The increase of recruitment is correlated to the extent of tissue damage at the beginning of the disease (Audoin et al. 2003). At advanced stages, when tissue damage is becoming too significant, brain activation decreases (Pantano et al. 2005) evidencing limits of the brain reorganization and the decrease of the cognitive resources

(Cader et al. 2006). A recovery of the functional activation pattern may occur over time in response to rehabilitation or pharmacological agents such as cholinergic treatments (Parry et al. 2003) or potassium channel blockers.

Upcoming studies try to combine measures of functional connectivity with measures of structural brain damage to improve the understanding of the relation between structural and functional abnormalities (Rocca et al. 2007, 2009) and therefore to better understand MS.

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) is a powerful non-invasive method to assess in vivo brain metabolism (Ross and Bluml 2001). MRS differs from the other MRI

Fig. 4 Functional imaging from a relapsing-remitting MS patient showing activations of primary and supplementary motor areas and sensoricortex during a hand motor task

techniques by the fact that the measured signal does not derive from protons of water but from protons of organic molecules. The main brain metabolites detected by MRS at long echo time ($TE > 135$ ms) are: N-acetyl aspartate (NAA) detected at 2 ppm, a neuronal marker; creatine/phosphocreatine (Cr) detected at 3 ppm, a marker of cellularity and energetic metabolism; choline compounds (Cho) detected at 3.2 ppm, a marker of membrane turn-over (e.g., demyelination/remyelination) and inflammation; and lactate (Lac), a marker of anaerobic metabolism and a substrate of macrophages. At short echo time ($TE < 40$ ms), other metabolites can be observed such as: myo-inositol (mIno) at 3.54 ppm, a marker of glial activation; glutamate/glutamine detected at 2.1–2.3 ppm, a marker of excitotoxicity; and macromolecules including lipids detected at 1.1–1.4 ppm, a marker of the membrane degradation products (e.g., demyelination) (Ross and Bluml 2001; Sajja et al. 2009).

In acute focal gadolinium-enhanced lesions, elevation of Cho, Lac, Cr, mIno, and lipids levels and reduction of NAA are observed (Davie et al. 1994; Arnold et al. 2000) (Fig. 5). In addition, glutamate levels rise suggesting a link between excitatory amino acids and axonal damage perhaps due to excitotoxicity (Srinivasan et al. 2005). Over time, within the lesions, the extent of recovery of these metabolites is highly variable. In most lesions, Lac, Cho, Cr, and lipids levels normalize after an initial increase, suggesting resorption of edema and remyelination process (Audoin et al. 2007c; De Stefano and Filippi 2007). Acute WM inflammation also impacts on GM NAA levels showing a global but transient dysfunction of neurons during inflammation (Van Au Duong et al. 2007). However, NAA may remain persistently low or may present only

Fig. 6 Susceptibility-weighted image acquired at 3T on a patient with early MS. Note the significant change of contrast in the MS lesion (arrow)

partial recovery indicating irreversible axonal damage or loss (De Stefano et al. 1995).

MRS can also detect diffuse microscopic damage in normal appearing WM and GM. In WM, diffuse metabolic damages are characterized by a decrease of NAA that likely reflects a loss of axonal integrity (axonal dysfunction and/or axonal loss) and an increase of Cho, lipids, and mIno mainly reflecting diffuse inflammation and gliosis (Husted et al. 1994; He et al. 2005). Such metabolic changes can

Fig. 5 Spectra representing the metabolic patterns in a focal inflammatory demyelinating lesion (a) and in a focal demyelinating lesion without inflammation (b)

occur several months before the appearance of gadolinium-enhancing lesions. Concerning diffuse metabolic changes in GM, decreased NAA and increased lipids have been observed, emphasizing demyelination process and loss of axonal integrity (Sharma et al. 2001; Chard et al. 2002; Sijens et al. 2006). Additional metabolites relevant to MS are under active investigation, such as glutathione, GABA, ascorbic acid, and macromolecules, especially components involved in the myelin sheaths. The quantification of such metabolites should provide insights into the roles of neurodegeneration, tissue repair, and antioxidant therapy in MS (Bakshi et al. 2008).

Longitudinal studies suggest that MRS measures hold promise in predicting the development of clinical disability (Sajja et al. 2009).

High field MR scanners

High field imaging ($\geq 3\text{T}$) and ultra high field imaging ($\geq 7\text{T}$), which increase the sensitivity of conventional and quantitative MRI techniques, are becoming relevant tools to better understand MS. For example, new MRI techniques like double inversion recovery (DIR) and susceptibility-weighted imaging (SWI) improve considerably the detection of cortical lesions in MS. DIR provides two different inversion pulses which attenuate the signal from cerebrospinal fluid and WM allowing the achievement of an important delineation between GM and WM. A recent study performed at 3T demonstrates the efficiency of the DIR technique to detect MS lesions with high sensitivity compared to conventional MRI especially in the infratentorial region (Wattjes et al. 2007). SWI uses a type of contrast different from traditional proton density, T_1 or T_2 imaging. This technique, using a fully flow compensated, long echo gradient echo sequence, exploits the susceptibility differences between tissues and uses the phase image to detect these differences. The magnitude and phase data are combined to produce an enhanced contrast (Fig. 6). At high magnetic field, due to increased susceptibility effects, SWI has the potential to provide higher contrast and contribute therefore to improve the examination of microscopic venous structures, brain iron, and microbleeds. For instance, SWI is becoming relevant to demonstrate detailed structural anatomy of MS lesions that are missed by conventional MRI (Haacke et al. 2009). At 3T, SWI has been useful to characterize a significantly reduced visibility of periventricular WM venous vasculature in patients with MS compared to control subjects (Ge et al. 2009). At 7T, the high sensitivity of SWI allows identification of a characteristic central vessel in visible MS lesions (Tallantyre et al. 2009). It appears that SWI could be used in the next future as a surrogate marker to investigate the

pathogenesis of MS lesions especially through assessment of microscopic vasculature and iron deposition changes.

The increasing availability of ultra high field MR scanners contributes to the improvement of the sensitivity of conventional and advanced MRI techniques and also to the emergence of new MRI techniques providing new features to better identify MS. For example, sodium imaging could be a powerful non-invasive tool to monitor the functional and structural integrity of axons in MS, by depicting the changes on the sodium concentration gradient between intra and extracellular space known to be an initial event leading to axonal degeneration (Fleysher et al. 2009).

Conclusion

Advanced MRI techniques such as magnetization transfer imaging, diffusion MRI, functional MRI, and magnetic resonance spectroscopy are powerful tools to better characterize and monitor the evolution of multiple sclerosis. Those quantitative techniques enable detection of focal and diffuse brain damage within the whole brain at the structural, functional, and metabolic levels. The overall data presented in this review demonstrate that the quantitative MRI metrics, especially when they correlate to clinical disability, allow a better understanding of MS. Longitudinal studies involving combination of these advanced MRI techniques with the assessment of clinical disability have to be performed at the individual level to better assess the evolution over time of the disease, and to evaluate the potential repair efficiency of proposed therapies like rehabilitation or new pharmaceutical drugs especially at the very early stage of MS.

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