**Background**

Damage to myelin, one of the major constituents of the white matter (WM), is considered the pathological hallmark of several congenital and acquired afflictions of the central nervous system (CNS), including errors of metabolism, multiple sclerosis (MS) and other inflammatory disorders, hypoxic-ischemic diseases, infections disease, intoxication and trauma. Several pathological studies have consistently demonstrated that demyelination, in combination with reduction in axon density, and decline in the number and length of myelinated fibers (Meier-Ruge et al. 1992; Marner et al. 2003), occurs also with aging. Clearly, these pathological abnormalities might turn out to be primarily a consequence of aging by itself or an accumulation of remote effects from lesions dispersed throughout the brain. Recent in-vivo MR-based studies have demonstrated an uneven distribution of WM abnormalities in healthy individuals with aging (Pagani et al., 2008), which is likely to reflect spatially specific vulnerability rooted in development. Human WM is characterized by a “heterochronologic” development since some regions myelinate on a different timeline than others (Huttenlocher and Dabholkar 1997), with heavily myelinated connections serving primary sensorimotor functions completing myelination first and having a high ratio of oligodendrocytes to myelinated fibers. Conversely, association fibers have longer period of myelin formation and one oligodendrocyte may myelinate multiple small fibers, resulting in thinner myelination (Bartzokis 2004). The increased vulnerability to aging of association cortices rather than sensory regions as well as the anterior-posterior gradient of such vulnerability support the theory that the impact of aging is predominant to the frontal lobes (Pfefferbaum et al. 2005), and might contribute to explain, at least partially, the preferential involvement of frontal lobe structure and function observed in several demyelinating neurological conditions, including MS.

Despite conventional MRI has been proven to be sensitive towards macroscopic related damage in the majority of the neurological conditions previously mentioned, it is unable to provide accurate estimates about the extent and nature of the associated tissue damage. During the past decades, several quantitative MR-based techniques, with increased pathological specificity to the heterogeneous substrates of CNS pathology, have been
developed and applied to improve the understanding of the pathophysiology of the above
diseases (in particular MS), as well as the understanding of the mechanisms responsible for
the accumulation of irreversible disability.

Possible areas of improvements
Dual-echo sequences have an high sensitivity towards macroscopic tissue changes in WM
diseases. However, several improvements still need to be achieved, in order to increase the
knowledge of the pathophysiology of these disorders, to understand their heterogeneous
spectra of clinical manifestations, and to monitor their course.
Possible areas of improvement are the following:

1) Better detection of grey matter (GM) demyelination.
2) Development of MR sequences which allow a better definition of areas of
demyelination in the spinal cord.
3) Definition of acquisition protocol for conventional and quantitative (magnetization
transfer and diffusion tensor MRI) MR-based techniques at high field strength
scanners.
4) Development of methods of analysis which allow to track the evolution profile in
single, newly formed lesions, in order to monitor processes of demyelination and
remyelination. Such an approach might be subsequently applied in the context of
pharmacological trials.
5) Development of myelin water fraction imaging at high field strengths (whole brain
coverage, 3D imaging).
6) Definition of composite scales, derived from the aggregation of different MR
techniques, sensitive towards different aspects of WM pathology, which may provide
a means to characterize overall disease severity in a more comprehensive and
clinically relevant way than can be obtained with individual MRI measures.
7) Development and application of spatially-specific voxel-based approaches to achieve a
topographical definition of atrophy, MT and DW changes in the WM and GM.
8) Linking measures of structural and functional damage, by combining analysis of
functional connectivity with tractography.

Suggested reading
Agosta F, Filippi M. MRI of spinal cord in multiple sclerosis. J Neuroimaging 2007;17:46S-
49S. Review.


