# AJNR

**Multiple Sclerosis and Alzheimer Disease through the Looking Glass of MR Imaging**

Giovanni B. Frisoni and Massimo Filippi

This information is current as of May 30, 2025.

# Review Article

# Multiple Sclerosis and Alzheimer Disease through the Looking Glass of MR Imaging

Giovanni B. Frisoni and Massimo Filippi

MR imaging has led to a profound shift of perspective in many central nervous system conditions. In epilepsy, quantitative evidence of hippocampal volume loss by MR imaging has been highly correlated with seizure onset in medial temporal structures (1); in stroke, it has enabled detection of the earliest structural changes and targeting of patients for thrombolysis (2); and in brain tumors, it has allowed unprecedented, accurate preoperative work-up (3). The field in which MR imaging has contributed most to shape current knowledge about the mechanisms leading to irreversible disability and, as a consequence, the identification of effective treatment, however, is perhaps multiple sclerosis (MS) and allied white matter diseases.

MR imaging also holds substantial promise to improve our understanding of Alzheimer disease (AD). Unfortunately, although the first attempts to image the typical medial temporal lobe damage of AD date back to 1992 (4, 5), little progress has since been made in other likely relevant aspects of the disease. Although it is believed that, by the time patients meet a diagnosis of AD, tissue damage has already spread from the medial temporal lobe to all neocortical regions (6), only recently in vivo changes of the most affected neocortical areas (ie, the temporoparietal junction and the posterior cingulate cortex) have been quantified by using MR imaging (7, 8). As a consequence, the detection of predementia changes by MR imaging is still a matter of active research (9). Moreover, although one of the 2 pathologic hallmarks of AD (neurofibrillary tangles, the other being senile plaques) is intracytoplasmic and is believed to disrupt axonal transport (10), white matter damage specific to AD has been only marginally investigated by using MR imaging. Finally, the ability of MR imaging to detect brain tissue loss in AD with great precision (7) has been used well below its potential to assess the efficacy of disease-modifying drugs in AD. In the following report, major advances in understanding the pathophysiology of MS through the use of MR imaging are discussed briefly and compared with what is currently being done in AD (Table).

## Understanding Disease Pathophysiology

There is an increasing body of evidence derived from both postmortem (11–13) and quantitative MR imaging (14–16) studies indicating that (a) MS is not simply the result of inflammatory demyelination, but that prominent neurodegeneration also occurs (13); (b) neurodegeneration starts very early in the course of the disease (14); and (c) inflammatory demyelination and neuroaxonal loss are only partially associated (14). Both of these 2 pathologic aspects of the disease contribute to the development of patients' symptoms and disability (17).

Similarly, AD neuropathology features not only neurodegeneration, but also inflammation. Positron-emission tomography (PET) and pathologic studies have shown that microglial activation is an important aspect of AD pathology (18, 19), which might develop as a reaction to amyloid deposition and is associated to the subsequent loss of cerebral tissue (20). Although these observations support the notion that inflammation might be a therapeutic target in AD (21), whether inflammation in AD is harmful or protective by promoting amyloid clearance (20) remains unclear. In light of its sensitivity to inflammatory changes and its noninvasivity, a more extensive use of modern MR imaging technology (eg, cellular MR imaging and perfusion MR imaging) is warranted to achieve a better understanding of the role of inflammation in AD.

## Diffuse Structural Tissue Damage

MS causes not only focal, T2-visible white matter lesions, which represent the "tip of the iceberg," but also diffuse white matter pathology, which is undetected by conventional MR imaging. This "occult" component of MS pathology has been shown in all MS phenotypes (22), including patients presenting with clinically isolated syndromes (CIS) suggestive of MS (15, 23). The extent of these occult abnormalities has been found to correlate better than the burden of focal lesions to the clinical manifestations of the disease, such as cognitive impairment (24). The nature of these changes is still unclear, but it is likely secondary to Wallerian degeneration of fibers passing through large white matter lesions or subtle chang-

**Contribution of MR imaging to understanding the pathophysiology of multiple sclerosis and Alzheimer disease**

|  | Multiple Sclerosis | Alzheimer's Disease |
|---|---|---|
| Disease pathophysiology | Neurodegeneration in addition to inflammation | Inflammation in addition to neurodegeneration |
| Diffuse structural tissue damage | Damage to normal-appearing white matter | Damage to normal-appearing gray matter |
| White/gray matter involvement | Damage to gray in addition to white matter | Damage to white in addition to gray matter |
| Earliest clinical phase | Prognostic value of multiple MR imaging lesions. Presence of neurodegeneration | Hippocampal atrophy as part of the "Alzheimer disease signature" |
| Cortical plasticity | Cortical reorganization following focal and diffuse tissue injury | Cortical reorganization possibly following plaque and tangle deposition |
| Monitoring treatment efficacy | MR imaging metrics are primary end points in phase II and secondary end points in phase III trials | MR imaging technology exploited only in most recent trials |

es—which can, however, include axonal loss (25)—beyond the resolution of commonly available scanners.

As is the case for MS (26), several MR imaging studies of patients with AD have shown that the correlation between regional gray matter atrophy and global cognitive impairment is relatively weak (27–29), which suggests that other pathologic processes such as microstructural gray and white matter damage might also play a significant role (27, 30). This is likely to be the result of structural and metabolic injury to neurons, which can eventually lead to neuronal death. A study based on the combined quantification of tissue loss of the hippocampus and damage of the remaining tissue has shown a strong correlation between cognitive impairment and MR imaging findings (31). There is, therefore, an urgent need to quantify the extent and define the nature of tissue damage of the AD brain beyond sensitivity of conventional MR imaging. A deeper appreciation of microstructural gray matter damage in AD might indeed provide precious diagnostic information at the earliest stages of the disease (9), account for the wide variability of memory performance in patients with similar degrees of hippocampal atrophy (32), and contribute to the definition of the neurobiologic substrates of clinically disruptive, but yet elusive, symptoms such as insomnia, agitation, and psychosis (33).

### White/Gray Matter Involvement

MS-related tissue damage is not limited to white matter, but also significantly involves the gray matter (22). Thus, MS should be viewed as a global brain pathology rather than a disease confined to the white matter. This notion is supported by both postmortem (11–13) and quantitative MR imaging (14–16) studies showing marked and evolving gray matter damage in patients with various MS phenotypes. Gray matter damage in MS might be secondary to neuronal loss due to retrograde degeneration or discrete gray matter lesions (12).

Similarly, AD pathology is not limited to the gray matter, but involves the white matter as well. Several studies, specifically designed to rule out white matter abnormalities of different origin, have shown that white matter areas linked to associative cortices are sites of tissue damage, which remains occult on con-

ventional MR imaging scans (34–36). These studies also found strong correlations between the extent and severity of white matter damage and AD-related cognitive decline (34, 36). White matter damage in AD can be either the consequence of abnormal axonal transport due to the presence of neurofibrillary tangles involving the cytoskeleton or, but not mutually exclusive, the result of anterograde axonal degeneration. The damage to the white matter specific to AD might add to the aspecific age-associated myelin breakdown occurring in late-myelinating association regions, such as the splenium and genu of the corpus callosum and contribute to the "dysconnection syndrome" of old age (37). This is a hypothetical scenario, however, that needs much deeper investigation. Alternatively, white matter damage might be caused by direct deposition of amyloid in the white matter (38).

### The Earliest Clinical Phase

The clinical onset of MS is frequently represented by a CIS, involving the optic nerve, the brain stem or the spinal cord. Identifying which patients with CIS will go on to develop definite MS and severe disability is a challenging task with important treatment implications. MR imaging can be of enormous help in this context, because it has been shown in a 14-year follow-up study, which strengthens previous observations based on shorter follow-up periods (39), that >80% of patients with CIS and MR imaging lesions go on to be diagnosed with MS, whereas approximately 20% have self-limited processes (40). This has led to the development of new diagnostic criteria that allow a diagnosis of MS to be made in a patient presenting with a CIS and appropriate MR imaging findings (41). The recent application of quantitative MR imaging technology to patients with CIS has convincingly shown that tissue loss is already present at this very early clinical stage of the disease (15) and that it progresses at a relatively rapid pace in the subsequent few months (14), thus indicating the need for early therapeutic intervention, with the potential to limit the irreversible consequences of MS-related tissue injury.

Seminal studies of patients with mild cognitive impairment, a condition progressing to AD in about half of the cases (9), and that can be viewed as having the

same relationship that CIS has with MS, have shown that a reduction of the size of the hippocampus is one of the most sensitive indicators of the full clinical development of the disease (42). Hippocampal atrophy alone, however, does not seem sufficient to predict progression with clinically satisfactory accuracy (9, 42). It is conceivable that a combination of this with other biologic markers of AD, such as high levels of tau protein in the CSF (43) and cortical metabolic defects on PET (44) or single-photon emission tomography (SPECT) (45), might be associated with an increased accuracy (9). In this context, the definition of novel MR-based markers with a high degree of prognostic accuracy would facilitate greatly a preclinical diagnosis of AD and would have treatment implications that might be paramount once disease-modifying drugs are available (46).

### Cortical Plasticity

Significant functional cortical reorganization takes place in MS, which is likely to have a role in limiting the impact of irreversible tissue damage on the clinical outcome (47). This is central to the development of new treatment strategies aimed at enhancing the natural capability of the human brain to respond to disease injury, thus reducing or delaying the development of "fixed" disability.

Significant functional cortical reorganization also takes place in AD, as suggested by a number of functional MR imaging studies (48–51) showing that, when performing cognitive tasks, patients activate larger cortical areas than cognitively intact elderly persons. Such cortical reorganization is believed to represent an attempt of the brain to compensate for the decreased function of the areas more affected by plaque and tangle pathology through enhanced recruitment of those that are still less affected. Empirical observations have shown that nonpharmacologic interventions alone (52) or in combination with cholinesterase inhibitors (Onder et al, personal communication) have a symptomatic effect in AD. The efficacy of these interventions might be better exploited if their functional neurobiology will be assessed more deeply.

### Monitoring Treatment Efficacy

During the past several years, 6 treatment options (3 interferon beta preparations, glatiramer acetate, mitoxantrone, and natalizumab) have been approved for treating MS. It is likely that this would not have occurred without the use of MR imaging as a surrogate outcome measure in the context of double-blind, randomized, placebo-controlled trials (53). At present, conventional MR imaging-derived metrics are used as additional measures of outcome in virtually all MS trials. Recent work is also showing that the application of modern quantitative MR technology is contributing significantly in elucidating whether and how experimental treatment works in MS (54).

Drugs presently licensed for use in patients with AD (donepezil, rivastigmine, galantamine, and me-

mantine) have been developed based on clinical trials designed in the 1990s with behavioral outcome measures (eg, cognitive performance, daily function, clinician-based impression of change) (55). Only more recent trials (56) have included MR imaging–measured brain atrophy as an additional outcome measure, and none has yet exploited the potential of quantitative MR techniques, such as proton MR spectroscopy and diffusion-weighted MR imaging. PET- and SPECT-based in vivo imaging with specific beta-amyloid tracers will likely bring a new and most significant tool to assess the efficacy of disease modifying drugs (57).

### Conclusion

During the past decade, MR imaging has contributed significantly to elucidate MS pathophysiology and improve clinical management and treatment monitoring of these patients. Extensive application of MR imaging technology is likely to be equally rewarding in the assessment of AD. Other neurodegenerative brain conditions—such as dementia with Lewy bodies, frontotemporal dementia, and multiple system atrophy, which share with AD the key pathophysiologic mechanisms of toxic protein deposition—might also benefit significantly. This calls for enhanced research activity in the field and, as a consequence, the need to allocate more resources to the application of MR imaging to AD and allied conditions.

### References

1. Spencer SS. **The relative contributions of MRI, SPECT, and PET imaging in epilepsy.** *Epilepsia* 1994;35:S72–S89
2. Parsons MW, Barber PA, Chalk J, et al. **Diffusion- and perfusion-weighted MRI response to thrombolysis in stroke.** *Ann Neurol* 2002;51:28–37
3. Rees J. **Advances in magnetic resonance imaging of brain tumours.** *Curr Opin Neurol* 2003;16:643–650
4. Jack CR Jr, Petersen RC, O'Brien PC, Tangalos EG. **MR-based hippocampal volumetry in the diagnosis of Alzheimer's disease.** *Neurology* 1992;42:183–188
5. Jobst KA, Smith AD, Szatmari M, et al. **Detection in life of confirmed Alzheimer's disease using a simple measurement of medial temporal lobe atrophy by computed tomography.** *Lancet* 1992;340:1179–1183
6. Smith AD. **Imaging the progression of Alzheimer pathology through the brain.** *Proc Natl Acad Sci USA* 2002;99:4135–4137
7. Ashburner J, Csernansky JG, Davatzikos C, et al. **Computer-assisted imaging to assess brain structure in healthy and diseased brains.** *Lancet Neurol* 2003;2:79–88
8. Frisoni GB, Testa C, Zorzan A, et al. **Detection of grey matter loss in mild Alzheimer's disease with voxel based morphometry.** *J Neurol Neurosurg Psychiatry* 2002;73:657–664
9. Frisoni GB, Padovani A, Wahlund L-O. **The predementia diagnosis of Alzheimer's disease.** *Alzheimer Dis Assoc Disord* 2004;18:51–53
10. Mandelkow EM, Stamer K, Vogel R, et al. **Clogging of axons by tau, inhibition of axonal traffic and starvation of synapses.** *Neurobiol Aging* 2003;24:1079–1085
11. van Waesberghe JH, Kamphorst W, De Groot CJ, et al. **Axonal loss in multiple sclerosis lesions: magnetic resonance imaging insights into substrates of disability.** *Ann Neurol* 1999;46:747–754
12. Peterson JW, Bo L, Mork S, et al. **Transected neurites, apoptotic neurons, and reduced inflammation in cortical multiple sclerosis lesions.** *Ann Neurol* 2001;50:389–400
13. Trapp BD, Ransohoff R, Rudick R. **Axonal pathology in multiple sclerosis: relationship to neurologic disability.** *Curr Opin Neurol* 1999;12:295–302

14. Filippi M, Rovaris M, Inglese M, et al. **Reduced brain tissue loss during randomised study of interferon β-1a in patients at presentation with syndromes suggestive of multiple sclerosis.** *Lancet* 2004;364:1489–1496

15. Filippi M, Bozzali M, Rovaris M, et al. **Evidence for widespread axonal damage at the earliest clinical stage of multiple sclerosis.** *Brain* 2003;126:433–437

16. Inglese M, Ge Y, Filippi M, et al. **Indirect evidence for early widespread gray matter involvement in relapsing remitting multiple sclerosis.** *NeuroImage* 2004;21:1825–1829

17. Coles AJ, Wing MG, Molyneux P, et al. **Monoclonal antibody treatment exposes three mechanisms underlying the clinical course of multiple sclerosis.** *Ann Neurol* 1999;46:296–304

18. Itagaki S, McGeer PL, Akiyama H, et al. **Relationship of microglia and astrocytes to amyloid deposits of Alzheimer disease.** *J Neuroimmunol* 1989;24:173–182

19. Cagnin A, Brooks DJ, Kennedy AM, et al. **In-vivo measurement of activated microglia in dementia.** *Lancet* 2001;358:461–467

20. Golde TE. **Inflammation takes on Alzheimer disease.** *Nat Med* 2002;8:936–938

21. Aisen PS. **The potential of anti-inflammatory drugs for the treatment of Alzheimer's disease.** *Lancet Neurol* 2002;1:279–284

22. Filippi M, Rovaris M, Comi G, eds. *Normal-appearing white and grey matter damage in multiple sclerosis.* Springer-Verlag: Milan;2004

23. Iannucci G, Rovaris M, Giacomotti L, et al. **Correlations between measures of multiple sclerosis pathology derived from T2, T1, magnetization transfer and diffusion tensor MR imaging.** *AJNR Am J Neuroradiol* 2001;22:1462–1467

24. Filippi M, Tortorella C, Rovaris M, et al. **Changes in the normal-appearing brain tissue and cognitive impairment in multiple sclerosis.** *J Neurol Neurosurg Psychiatry* 2000;68:157–161

25. Evangelou N, Esiri MM, Smith S, et al. **Quantitative pathological evidence for axonal loss in normal appearing white matter in multiple sclerosis.** *Ann Neurol* 2000;47:391–395

26. Rovaris M, Filippi M. **Magnetic resonance techniques to monitor disease evolution and treatment trial outcomes in multiple sclerosis.** *Curr Opin Neurol* 1999;12:337–344

27. Bozzali M, Falini A, Franceschi M, et al. **White matter damage in Alzheimer's disease assessed in vivo using diffusion tensor magnetic resonance imaging.** *J Neurol Neurosurg Psychiatry* 2002;72:742–746

28. Jack CR, Dickson DW, Parisi JE, et al. **Antemortem MRI findings correlate with hippocampal neuropathology in typical aging and dementia.** *Neurology* 2002;58:750–757

29. Laakso MP, Hallikainen M, Hanninen T, et al. **Diagnosis of Alzheimer's disease: MRI of the hippocampus vs delayed recall.** *Neuropsychologia* 2000;38:579–584

30. Meyerhoff DJ, MacKay S, Constans JM, et al. **Axonal injury and membrane alterations in Alzheimer's disease suggested by in vivo proton magnetic resonance spectroscopic imaging.** *Ann Neurol* 1994;36:40–47

31. Hanyu H, Asano T, Iwamoto T, et al. **Magnetization transfer measurements of the hippocampus in patients with Alzheimer's disease, vascular dementia, and other types of dementia.** *AJNR Am J Neuroradiol* 2000;21:1235–1242

32. Mori E, Yoneda Y, Yamashita H, et al. **Medial temporal structures relate to memory impairment in Alzheimer's disease: an MRI volumetric study.** *J Neurol Neurosurg Psychiatry* 1997;63:214–221

33. Robert PhH, Verhey FRJ, Byrne EJ, et al. **Grouping for behavioural and psychological symptoms in dementia: clinical and biological aspects: consensus paper of the European Alzheimer's Disease Consortium (EADC).** *Eur Psychiatry* 2005 (in press)

34. Hanyu H, Asano T, Sakurai H, et al. **Diffusion-weighted and magnetization transfer imaging of the corpus callosum in Alzheimer's disease.** *J Neurol Sci* 1999;167:37–44

35. MacKay S, Meyerhoff DJ, Constans JM, et al. **Regional gray and white matter metabolite differences in subjects with AD, with subcortical ischemic vascular dementia, and elderly controls with 1H magnetic resonance spectroscopic imaging.** *Arch Neurol* 1996;53:167–74

36. Yoshiura T, Mihara F, Ogomori K, et al. **Diffusion tensor in posterior cingulate gyrus: correlation with cognitive decline in Alzheimer's disease.** *Neuroreport* 2002;13:2299–2302

37. Bartzokis G, Sultzer D, Lu PH, et al. **Heterogeneous age-related breakdown of white matter structural integrity: implications for cortical "disconnection" in aging and Alzheimer's disease.** *Neurobiol Aging* 2004;25:843–851

38. Uchihara T, Kondo H, Akiyama H, Ikeda K. **White matter amyloid in Alzheimer's disease brain.** *Acta Neuropathol* 1995;90:51–56

39. Filippi M. **Magnetic resonance imaging findings predicting subsequent disease course in patients at presentation with clinically isolated syndromes suggestive of multiple sclerosis.** *Neurol Sci* 2001;22:S49–S51

40. Brex PA, Ciccarelli O, O'Riordan JI, et al. **A longitudinal study of abnormalities on MRI and disability from multiple sclerosis.** *N Engl J Med* 2002;346:158–164

41. McDonald WI, Compston A, Edan G, et al. **Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the Diagnosis of Multiple Sclerosis.** *Ann Neurol* 2001;50:121–127

42. Jack CR Jr, Petersen RC, Xu YC, et al. **Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment.** *Neurology* 1999;52:1397–1403

43. Riemenschneider M, Lautenschlager N, Wagenpfeil S, et al. **Cerebrospinal fluid tau and beta-amyloid 42 proteins identify Alzheimer disease in subjects with mild cognitive impairment.** *Arch Neurol* 2002;59:1729–1734

44. Chetelat G, Desgranges B, De La Sayette V, et al. **Mild cognitive impairment: can FDG-PET predict who is to rapidly convert to Alzheimer's disease?** *Neurology* 2003;60:1374–1377

45. Okamura N, Arai H, Maruyama M, et al. **Combined analysis of CSF tau levels and [(123)I]iodoamphetamine SPECT in mild cognitive impairment: implications for a novel predictor of Alzheimer's disease.** *Am J Psychiatry* 2002;159:474–476

46. Citron M. **Alzheimer's disease: treatments in discovery and development.** *Nat Neurosci* 2002;5:1055–1057

47. Filippi M, Rocca MA. **Cortical reorganisation in patients with MS: using functional MRI techniques to study patients with MS.** *J Neurol Neurosurg Psychiatry* 2004;75:1087–1089

48. Saykin AJ, Flashman LA, Frutiger SA, et al. **Neuroanatomic substrates of semantic memory impairment in Alzheimer's disease: patterns of functional MRI activation.** *J Int Neuropsychol Soc* 1999;5:377–392

49. Prvulovic D, Hubl D, Sack AT, et al. **Functional imaging of visuospatial processing in Alzheimer's disease.** *Neuroimage* 2002;17:1403–1414

50. Lustig C, Snyder AZ, Bhakta M, et al. **Functional deactivations: change with age and dementia of the Alzheimer type.** *Proc Natl Acad Sci USA* 2003;100:1454–1459

51. Dickerson BC, Salat DH, Bates JF, et al. **Medial temporal lobe function and structure in mild cognitive impairment.** *Ann Neurol* 2004;56:27–35

52. De Vreese LP, Neri M, Fioravanti M, et al. **Memory rehabilitation in Alzheimer's disease: a review of progress.** *Int J Geriatr Psychiatry* 2001;16:794–809

53. Barkhof F, Filippi M, Miller DH, et al. **Strategies for optimizing MRI techniques aimed at monitoring disease activity in multiple sclerosis treatment trials.** *J Neurol* 1997;244:76–84

54. Filippi M, Grossman RI. **MRI techniques to monitor MS evolution: the present and the future.** *Neurology* 2002;58:1147–1153

55. Mayeux R, Sano M. **Treatment of Alzheimer's disease.** *N Engl J Med* 1999;341:1670–1679

56. Growdon JH. **Incorporating biomarkers into clinical drug trials in Alzheimer's disease.** *J Alzheimers Dis* 2001;3:287–292

57. Nordberg A. **PET imaging of amyloid in Alzheimer's disease.** *Lancet Neurol* 2004;3:519–527