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MRI correlates of cognitive dysfunction in multiple sclerosis patients

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Studies with conventional magnetic resonance imaging (MRI) support the hypothesis that cognitive impairment in multiple sclerosis (MS) patients is related with the lesion burden. Patterns of frontal lobe cognitive decline were also found to be related with the corresponding regional lesion load, although the total lesion load on T_2-weighted MRI scans of the brain seems to be more relevant in determining frontal lobe deficits. Other non-conventional MRI techniques with a higher specificity to the heterogeneous substrates of MS pathology, such as the assessment of hypointense lesion load on T_1-weighted scans and the histogram analysis of magnetisation transfer ratio (MTR) maps, have recently been applied to MS cognitive studies. Results from these studies suggest that three factors play a role in the pathogenesis of MS dementia: the burden of MS lesions, the severity of the pathological damage within individual lesions and that of the normal-appearing white matter. *Journal of NeuroVirology* (2000) **6,** S172–S175.

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Introduction

The use of brain magnetic resonance imaging (MRI) for monitoring disease evolution in patients with multiple sclerosis (MS) is still hampered by the highly variable correlation with clinical findings (Filippi *et al*, 1995; Gass *et al*, 1994; Miller *et al*, 1998; Truyen *et al*, 1997; van Walderveen *et al*, 1995). In most of the studies, the change of disability over time is only partially explained by the corresponding conventional T_2-weighted brain MRI changes (Gass *et al*, 1994; IFNB MS Study Group, 1995). This clinical-MRI discrepancy has several explanations. The low reliability and precision of the Extended Disability Status Scale (Kurtzke, 1983) (EDSS) and the poor pathological specificity of conventional T_2-weighted MRI scans (Miller *et al*, 1998) are perhaps the most important. In addition, EDSS (Kurtzke, 1983) is heavily weighted towards locomotor disability, which is more likely due to spinal cord lesions.

The evaluation of cognitive functions in MS might overcome some of these deficiencies. Some degree of cognitive impairment can be detected in 40–60% of MS patients (Rao *et al* 1991; Ron *et al*, 1991), depending on both clinical and demographic characteristics of the sample studied and the neuropsychological tests administered. The assessment of the correlation between cognitive deficits and the extent and location of the abnormalities seen by MRI techniques may also provide new insights into the mechanisms underlying the development of 'fixed' disability in patients with MS. In this review, the results of recent quantitative MRI studies correlating the degree of cognitive impairment in patients with MS with the extent and the severity of the brain abnormalities seen using MRI techniques are presented and discussed with the ultimate goal of a better understanding of the pathophysiological mechanisms underlying the development of such deficits.

Correlations between conventional MRI abnormalities and cognitive dysfunction

In patients with MS, the extent of white matter abnormalities detected on conventional brain MRI scans correlates well with the performance on a wide variety of neuropsychological tests and the degree of this correlation is higher than that found with physical disability (Arnett *et al*, 1994; Foong *et al*, 1997; Rao *et al*, 1989; Swirsky-Sacchetti *et al*, 1992). Rao *et al* (1989) correlated neuropsychologi-

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cal tests performance with brain total T_2 lesion area (TLA) in 53 MS patients. They found that TLA was a robust predictor of cognitive dysfunction, particularly for measures of recent memory, abstract/conceptual reasoning, language, and visuo-spatial problem solving. In detail, 10 of 12 (83%) patients with TLA greater than 30 cm^2 had some degree of cognitive impairment, whilst 32 of 41 patients with TLA less than 30 cm^2 were cognitively intact. These results have been confirmed by several other investigators (Arnett *et al*, 1994; Foong *et al*, 1997; Rovaris *et al*, 1998; Swirsky-Sacchetti *et al*, 1992) and suggest that the widespread damage of the deep white matter may lead to functional disconnection of different cortical areas and of deep grey matter structures, such as the thalamus and the hippocampus, with, as a consequence, the development of cognitive deficits.

Correlations between regional MRI abnormalities and specific patterns of cognitive decline

Several studies assessed, using conventional T_2-weighted scanning, whether specific patterns of cognitive decline were the result of lesion location in specific sites of the hemispheric white matter (Arnett *et al*, 1994; Foong *et al*, 1997; Miki *et al*, 1998; Rovaris *et al*, 1998; Swirsky-Sacchetti *et al*, 1992). Swirsky-Sacchetti *et al* (1992) found that frontal lobe involvement best predicted the impairment of abstract problem solving, memory, and word fluency and that left parieto-occipital involvement best predicted deficits in verbal learning and complex visual-integrative skills. Arnett *et al* (1994) reported a significant correlation between the frontal lesion area on T_2-weighted scans and the performance on neuropsychological tests selectively exploring the frontal lobe functions. Foong *et al* (1997) and Rovaris *et al* (1998) found a significant correlation between frontal lobe impairment and frontal lesion volumes on T_2-weighted MRI scans. However, in this study, the contribution of total brain MRI lesion load to impairment of frontal lobe functions was found to be, at least, of the same relevance. Miki *et al* (1998) evaluated the frequency and location of lesions in the U-fibres and correlated these findings with neuropsychological impairment. Forty-two of such lesions were detected in 28 of the 53 patients studied (53%). The majority of them were in the frontal lobe (about 65%). Scores of neuropsychological tests reflecting performance in executive control and memory were significantly different between the patients with multiple U-fibre lesions and those without any or with only a single U-fibre lesion.

All these data provide evidence that specific lesion locations may account for the presence and the characteristics of cognitive decline in MS. However, some of these studies (Foong *et al*, 1997; Rovaris *et al*, 1998) also showed that the extent of overall brain and regional damage are strongly correlated, thus suggesting that specific brain area involvement and the consequent pattern of cognitive deficits may just be the results of a stochastic process. This, together with the known difficulties in segmenting accurately specific brain areas and in performing tests assessing individual cognitive domains specifically, may explain why the degree of correlations between regional MRI abnormalities and specific patterns of cognitive decline is sometimes disappointing.

Correlations between non-conventional MRI findings and cognitive dysfunction

All the studies reviewed in the previous paragraphs used MRI measures derived from conventional imaging. However, conventional T_2-weighted imaging gives little information about the pathological substrates of MS lesions, which ranges from oedema and inflammation to severe demyelination and axonal loss (Bruck *et al*, 1997; Lucchinetti *et al*, 1996; McDonald *et al*, 1992; Trapp *et al*, 1998). Although all these pathologies are characterised by an increased water content, giving hyperintense lesions on T_2-weighted MR images, they can, of course, result in different neurological outcomes. In addition, lesion load estimates from conventional imaging are known not to give a complete picture of the burden of disease (Filippi and Miller, 1996). Several studies, using different MRI techniques, showed that microscopic damage in the normal-appearing white matter (NAWM), which is not detected by conventional imaging (Filippi *et al*, 1995; Fu *et al*, 1998; Loevner *et al*, 1995; Narayanan *et al*, 1997) may account for some of the disability in MS (Filippi *et al*, 1995; Fu *et al*, 1998).

Recently, several MRI techniques, with the potential for higher pathological specificity, have been used to monitor MS (Miller *et al*, 1998). MS lesions visible as 'black holes' on T_1-weighted scans are thought to represent areas with severe tissue disruption (Bruck *et al*, 1997; van Walderveen *et al*, 1998). Low magnetisation transfer (MT) ratio (MTR) indicates a reduced capacity of the macromolecules in brain tissue to exchange magnetisation with the surrounding water molecules, thus reflecting damage to myelin or to the axonal membrane (McGowan *et al*, 1998). In MS patients, T_1-weighted hypointense MRI lesion load (Truyen *et al*, 1997; van Walderveen *et al*, 1995) and average lesion MTR (Gass *et al*, 1994) correlate better with physical disability than does the volume of abnormalities on conventional T_2-weighted MRI. MTR is also reduced in the normal appearing white matter (NAWM) of MS patients (Filippi *et al*, 1995; Loevner *et al*, 1995). Estimates of the amount and severity of microscopic and macroscopic disease burden can be obtained using MTR histograms (van Buchem *et al*, 1996), which may provide a more global picture of disease burden in MS.

Rovaris *et al* (1998) correlated the extent of abnormalities detected by T_2-, T_1-weighted and MT imaging (MTI) with the overall cognitive, frontal lobe, and memory impairments in 30 patients with MS and variable clinical courses. This study confirmed that the extent of brain damage, as measured on conventional MRI scans, is correlated with the degree of cognitive decline in MS. However, contrary to the expectations, no significant differences in T_1-weighted lesion loads were found between cognitively impaired and unimpaired patients. This result might be secondary to the intrinsic limitations of T_1 lesion load measurements (i.e., the amount of MS lesion visible on T_1-weighted scans is dependent on the acquisition parameters used and on the subjective evaluation of the rater) or to the heterogeneous sample of patients studied, which also included patients with primary progressive MS.

The situation was different when cognitive decline was correlated with MTI findings (Rovaris *et al*, 1998). Patients with frontal lobe and overall cognitive impairment had significantly higher MTI lesion loads and lower average lesion MTR than patients without any kind of cognitive impairment. This was also found for the mean MTR of the overall brain tissue studied with the MTR histogram analysis. Similar results were found in another study (van Buchem *et al*, 1998), where MTI findings were correlated with cognitive performances in 44 patients with MS. In this study, the results of many individual neuropsychological tests were correlated with MTI measures and the strengths of the correlations ranged from moderate to good. More recently, Comi *et al* (1999) compared T_2- and T_1-weighted MRI and MTI findings from two groups of MS patients, with or without evidence of frontal lobe impairment, who were matched for all the other clinical variables. In this study, total and frontal T_2- and T_1-weighted MRI lesion volumes were both significantly higher in cognitively impaired patients than in the others. Average MTR, peak height and location of whole brain, frontal lobe and cortical/subcortical region MTR histograms were all significantly lower for cognitively impaired than for cognitively intact patients, while cerebellar MTR histogram-derived metrics did not significantly differ between the two groups of patients. In another study (Filippi *et al*, 2000), MTR histogram analysis of the normal-appearing brain tissue (NABT) was obtained and a multivariate analysis of several MRI and MTI variables revealed that average MTR of the NABT was the factor that was most significantly associated with cognitive impairment in MS patients.

Conclusions

All these data indicate that the extent and severity of the macroscopic and microscopic brain changes are relevant in determining cognitive decline in MS. Nevertheless, many other aspects of the correlation between cognitive decline and MRI abnormalities still need to be elucidated. These include: (1) The predictive value of the abnormalities detected using different MRI techniques and the strengths of the correlations between changes over time of neuropsychological and MRI abnormalities. (2) The contribution of other non-conventional MRI techniques, such as MR spectroscopy and diffusion imaging, to the understanding of the cognitive decline in MS. (3) The contribution to the cognitive decline of juxta-cortical abnormalities, studied using fluid-attenuated inversion recovery (FLAIR) sequences, which have been shown to depict better such abnormalities than conventional T_2-weighted scans (Filippi *et al*, 1996). (4) The application of functional MRI to increase our understanding of the role of cortical disconnection and recovery mechanisms in determining or preventing the development of cognitive decline.

References

Arnett PA, Rao SM, Bernardin L, Grafman J, Yetkin FZ, Lobeck L (1994). Relationship between frontal lobe lesions and Wisconsin Card Sorting Test performance in patients with multiple sclerosis. *Neurology* **44:** 420–425.

Bruck W, Bitsch A, Kolenda H, Bruck Y, Stiefel M, Lassmann H (1997). Inflammatory central nervous system demyelination: correlation of magnetic resonance imaging findings with lesion pathology. *Ann Neurol* **42:** 783–793.

Comi G, Rovaris M, Possa F, Iannucci G, Santuccio G, Minicucci L, Filippi M (1999). Multiparametric MRI study of frontal lobe dementia in multiple sclerosis. *J Neurol* **246** (Suppl 1): I/62.

Filippi M, Miller DH (1996). MRI in the differential diagnosis and monitoring the treatment of multiple sclerosis. *Curr Opin Neurol* **9:** 178–186.

Filippi M, Campi A, Dousset V, Baratti C, Martinelli V, Canal N, Scotti G, Comi G (1995). A magnetization transfer imaging study of normal-appearing white matter in multiple sclerosis. *Neurology* **45:** 478–482.

Filippi M, Horsfield MA, Tofts PS, Barkhof F, Thompson AJ, Miller DH (1995). Quantitative assessment of MRI lesion load in monitoring the evolution of multiple sclerosis. *Brain* **118:** 1601–1612.

Filippi M, Tortorella C, Rovaris M, Bozzali M, Possa F, Iannucci G, Comi G (2000). Changes in the normal appearing brain tissue and cognitive impairment in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **68:** 157–176.

Filippi M, Yousry T, Baratti C, Becker C, Mammi S, Voltz R, Horsfield MA, Spaler S, Campi A, Reiser MF, Comi G (1996). Quantitative assessment of MRI lesion load in multiple sclerosis. A comparison of conventional spin-echo with fast fluid-attenuated inversion recovery. *Brain* **119:** 1349–1355.

Foong J, Rozewicz L, Quaghebeur G, Davie CA, Kartsounis LD, Thompson AJ, Miller DH, Ron MA (1997). Executive functions in multiple sclerosis. The role of frontal lobe pathology. *Brain* **120:** 15–26.

Fu L, Matthews PM, De Stefano N, Worsley KJ, Narayanan S, Francis GS, Antel JP, Wolfson C, Arnold DL (1998). Imaging of axonal damage of normal appearing white matter in multiple sclerosis. *Brain* **121:** 103–113.

Gass A, Barker GJ, Kidd D, Thorpe JW, MacManus DG, Brennan A, Tofts PS, Thompson AJ, McDonald WI, Miller DH (1994). Correlation of magnetization transfer ratio with disability in multiple sclerosis. *Ann Neurol* **36:** 62–67.

Kurtzke JF (1983). Rating neurological impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* **33:** 1444–1452.

Loevner LA, Grossman RI, Cohen JA, Lexa FJ, Kessler D, Kolson DL (1995). Microscopic disease in normal-appearing white matter on conventional MR imaging in patients with multiple sclerosis: assessment with magnetization-transfer measurements. *Radiology* **96:** 511–515.

Lucchinetti CF, Bruck W, Rodriguez M, Lassmann H (1996). Distinct patterns of multiple sclerosis pathology indicated heterogeneity in pathogenesis. *Brain Pathol* **6:** 259–274.

McDonald WI, Miller DH, Barnes D (1992). The pathological evolution of multiple sclerosis. *Neuropathol Appl Neurobiol* **18:** 319–334.

McGowan JC, Filippi M, Campi A, Grossman RI (1998). Magnetisation transfer imaging: theory and application to multiple sclerosis. *J Neurol Neurosurg Psychiatry* **64** (Suppl 1): S66–S69.

Miki Y, Grossman RI, Udepa JK, Wei L, Kolson DL, Mannon LJ, Grossman M (1998). Isolated U-fiber involvement in MS. Preliminary observations. *Neurology* **50:** 1301–1306.

Miller DH, Grossman RI, Reingold SC, McFarland (1998). The role of magnetic resonance techniques in understanding and managing multiple sclerosis. *Brain* **121:** 3–24.

Narayanan S, Fu L, Pioro E, De Stefano N, Collins DL, Francis GS, Antel JP, Matthews PM, Arnold DL (1997). Imaging of axonal damage in multiple sclerosis: spatial distribution of magnetic resonance imaging lesions. *Ann Neurol* **41:** 385–391.

Rao SM, Leo GJ, Bernardin L, Unverzagt F (1991). Cognitive dysfunction in multiple sclerosis: frequency, patterns and prediction. *Neurology* **41:** 685–691.

Rao SM, Leo GJ, Haughton VM, St. Aubin-Faubert P, Bernardin L (1989). Correlation of magnetic resonance imaging with neuropsychological testing in multiple sclerosis. *Neurology* **39:** 161–166.

Ron MA, Callanan MM, Warrington EK (1991). Cognitive abnormalities in multiple sclerosis: a psychometric and MRI study. *Psychol Med* **21:** 59–68.

Rovaris M, Filippi M, Falautano M, Minicucci L, Rocca MA, Martinelli V, Comi G (1998). Relation between MR abnormalities and patterns of cognitive impairment in multiple sclerosis. *Neurology* **50:** 1601–1608.

Swirsky-Sacchetti T, Mitchell DR, Seward J, Seward J, Gonzales C, Lublin F, Knobler R, Field HL (1992). Neuropsychological and structural brain lesions in multiple sclerosis: a regional analysis. *Neurology* **42:** 1291–1295.

The IFNB Multiple Sclerosis Study Group, the University of British Columbia MS/MRI Analysis Group (1995). Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. *Neurology* **45:** 1277–1285.

Trapp BD, Peterson J, Ransohoff RM, Rudick R, Mork S, Bo L (1998). Axonal transection in the lesions of multiple sclerosis. *N Eng J Med* **338:** 278–285.

Truyen L, van Waesberghe JHTM, van Walderveen MAA, van Oosten BW, Polman CH, Hommes OR, Adèr HJA, Barkhof F (1997). Accumulation of hypointense lesions ('black holes') on T1 spin-echo MRI correlates with disease progression in multiple sclerosis. *Neurology* **47:** 1469–1476.

van Buchem MA, Grossman RI, Armstrong C, Polansky M, Miki Y, Heyning FH, Boncoeur-Martel MP, Wei L, Udupa JK, Grossman M, Kolson DL, McGowan JC (1998). Correlation of volumetric magnetization transfer imaging with clinical data in MS. *Neurology* **50:** 1609–1617.

van Buchen MA, McGowan JC, Kolson DL, Polansky M, Grossman RI (1996). Quantitative volumetric magnetization transfer analysis in multiple sclerosis: estimation of macroscopic and microscopic disease burden. *Magn Reson Med* **36:** 632–636.

van Walderveen MAA, Barkhof F, Hommes OR, Polman CH, Tobi H, Frequin STFM, Valk J (1995). Correlating MRI and clinical disease activity in multiple sclerosis: relevance of hypointense lesions on short TR/short TE (T1-weighted) spin-echo images. *Neurology* **45:** 1684–1690.

van Walderveen MAA, Kamphorst W, Scheltens P, van Waesberghe JHTM, Ravid R, Valk J, Polman Ch, Barkhof F (1998). Histopathologic correlate of hypointense lesions on T1-weighted spin-echo MRI in multiple sclerosis. *Neurology* **50:** 1282–1288.